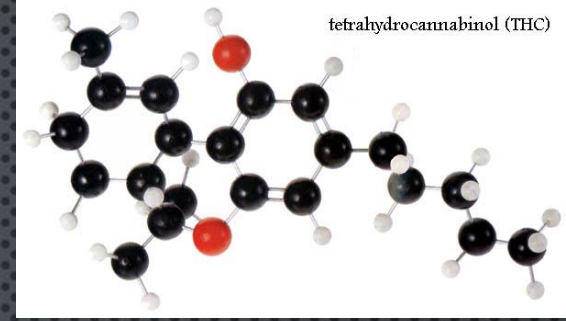


# Public Health Impact of Marijuana on Brain and Functioning

John F. Kelly, Ph.D.

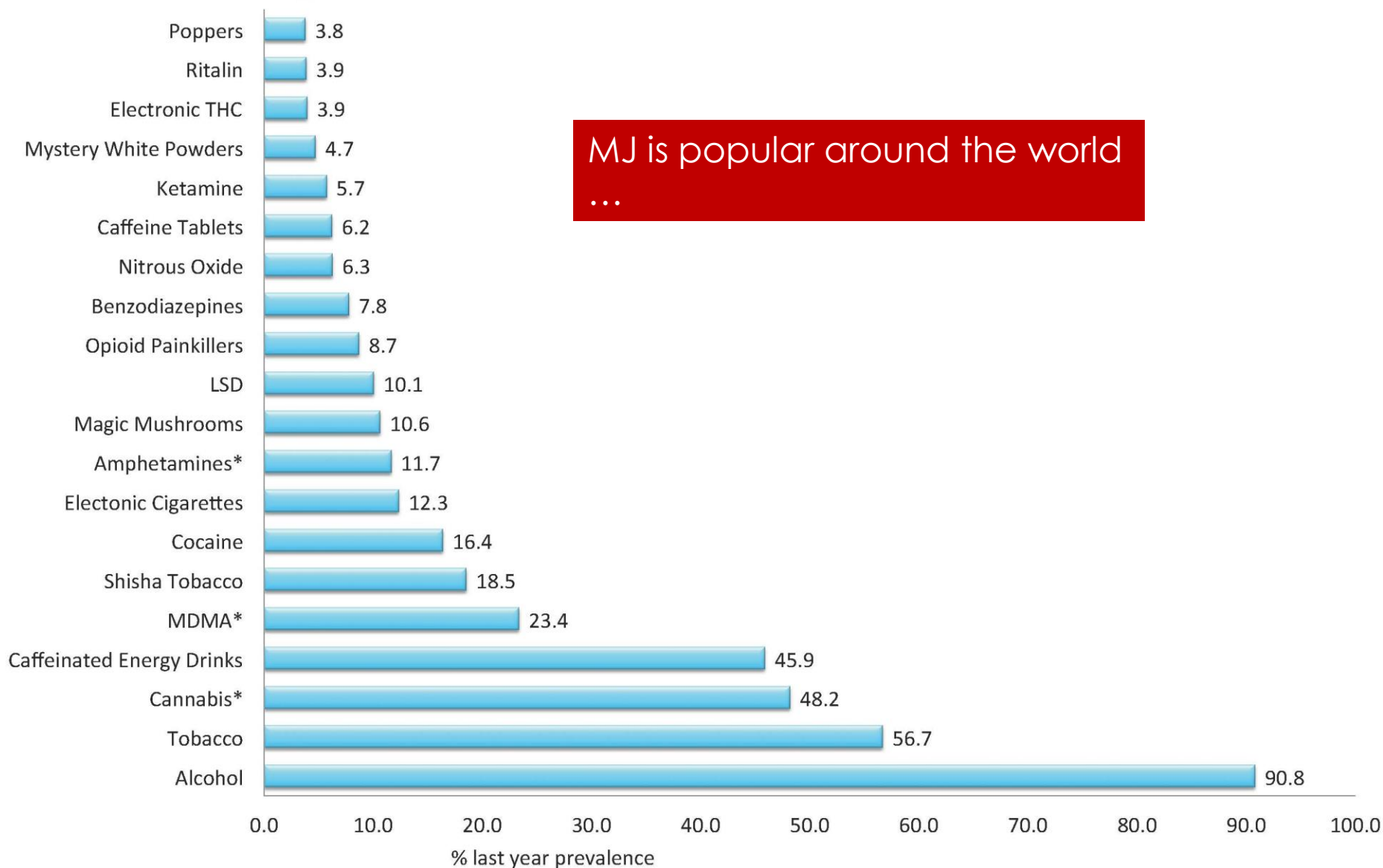
# WHAT IS MARIJUANA?

## KEY POINTS:

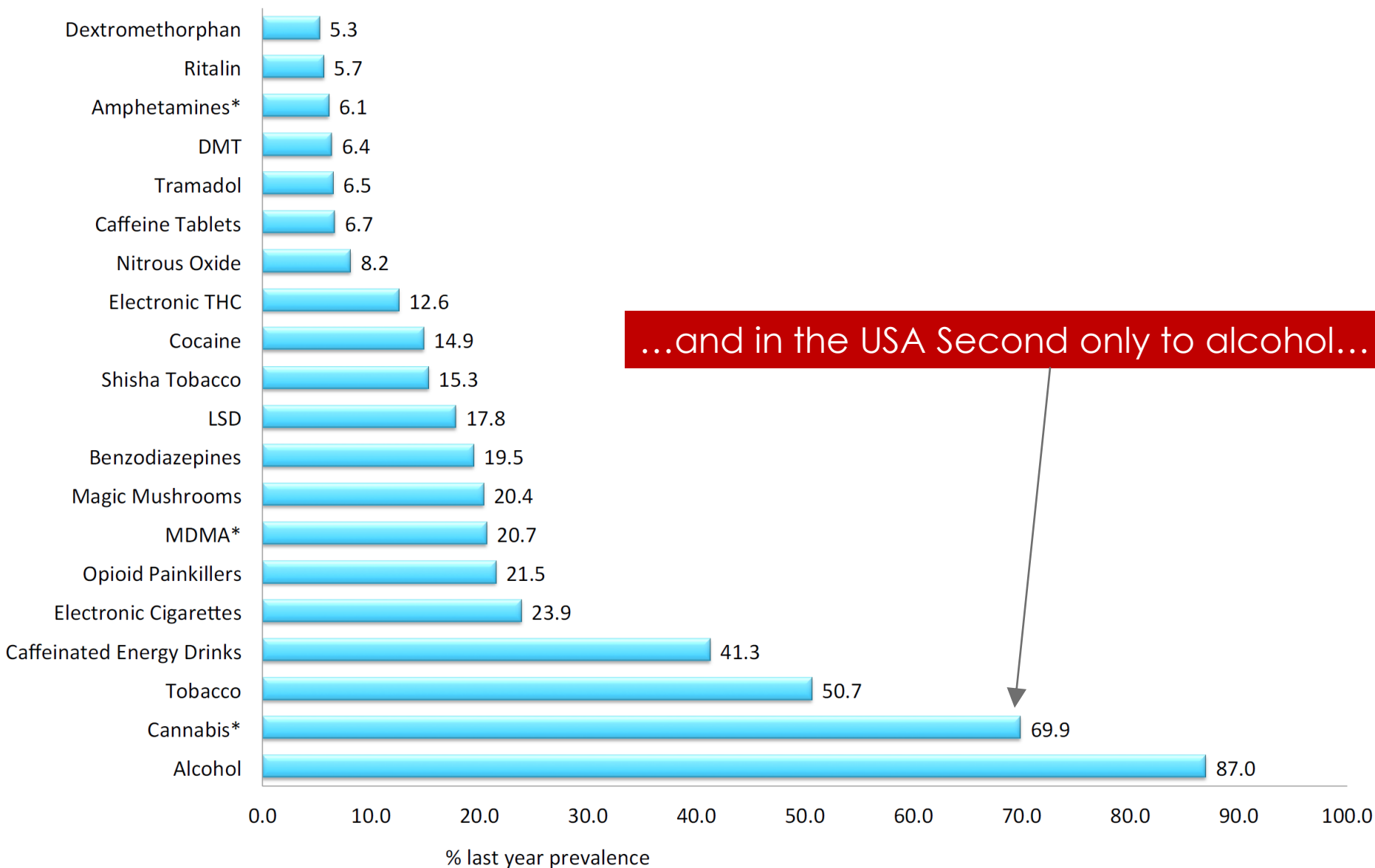


- NAME FOR CANNABIS SATIVA PLANT WHICH CONTAINS PSYCHOACTIVE EFFECTS THROUGH A VARIETY OF CANNABINOLS, NOTABLY DELTA-9 THC, AND CANNABIDIOL
- MOST COMMONLY INHALED THROUGH LUNGS, PRODUCES MILD EUPHORIA, MOOD ENHANCEMENT, RELAXATION; HIGHER/REGULAR USE PRODUCES INTOXICATION, SLOWED COGNITION/MEMORY IMPAIRMENT (SHORT-TERM MEMORY/WORKING MEMORY) INCREASED ANXIETY/PARANOIA/PSYCHOSIS, HALLUCINATIONS; ADDICTION
- CAN INCREASE THE LIKELIHOOD OF ACCIDENTS/MJ-RELATED DEATHS BUT UNLIKELY TO PRODUCE OD-RELATED MORTALITY DIRECTLY
- MAY BE NEUROTOXIC IN HIGHER DOSES; DEVELOPING/TEEN BRAIN MORE SUSCEPTIBLE TO NEGATIVE IMPACTS THAN OLDER ADULT USERS

# Top 20 Drugs – Last 12 Months – Whole Sample (N=78,819)



# Top 20 Drugs – Last 12 Months – USA (N=6,500)

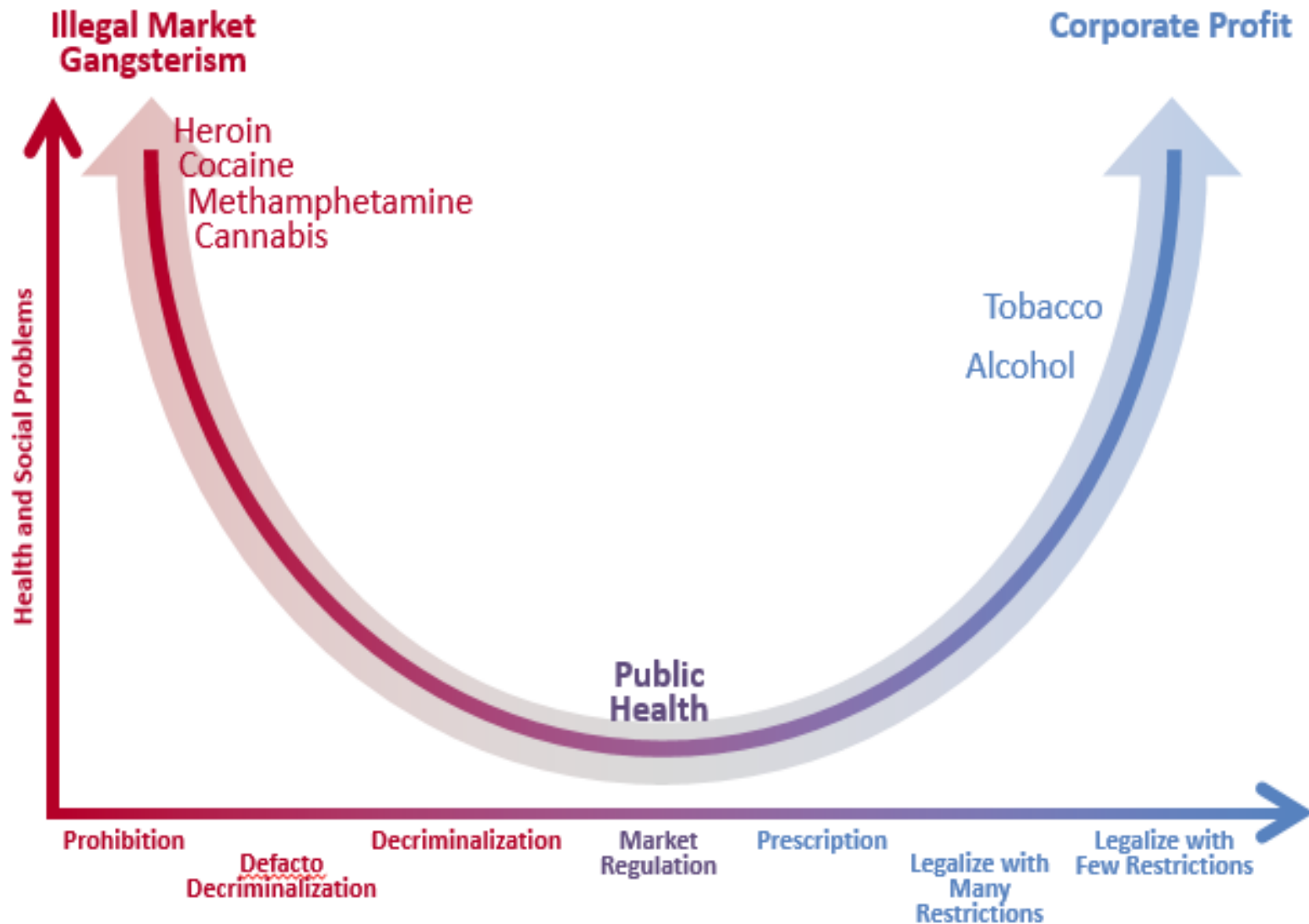


...and in the USA Second only to alcohol...

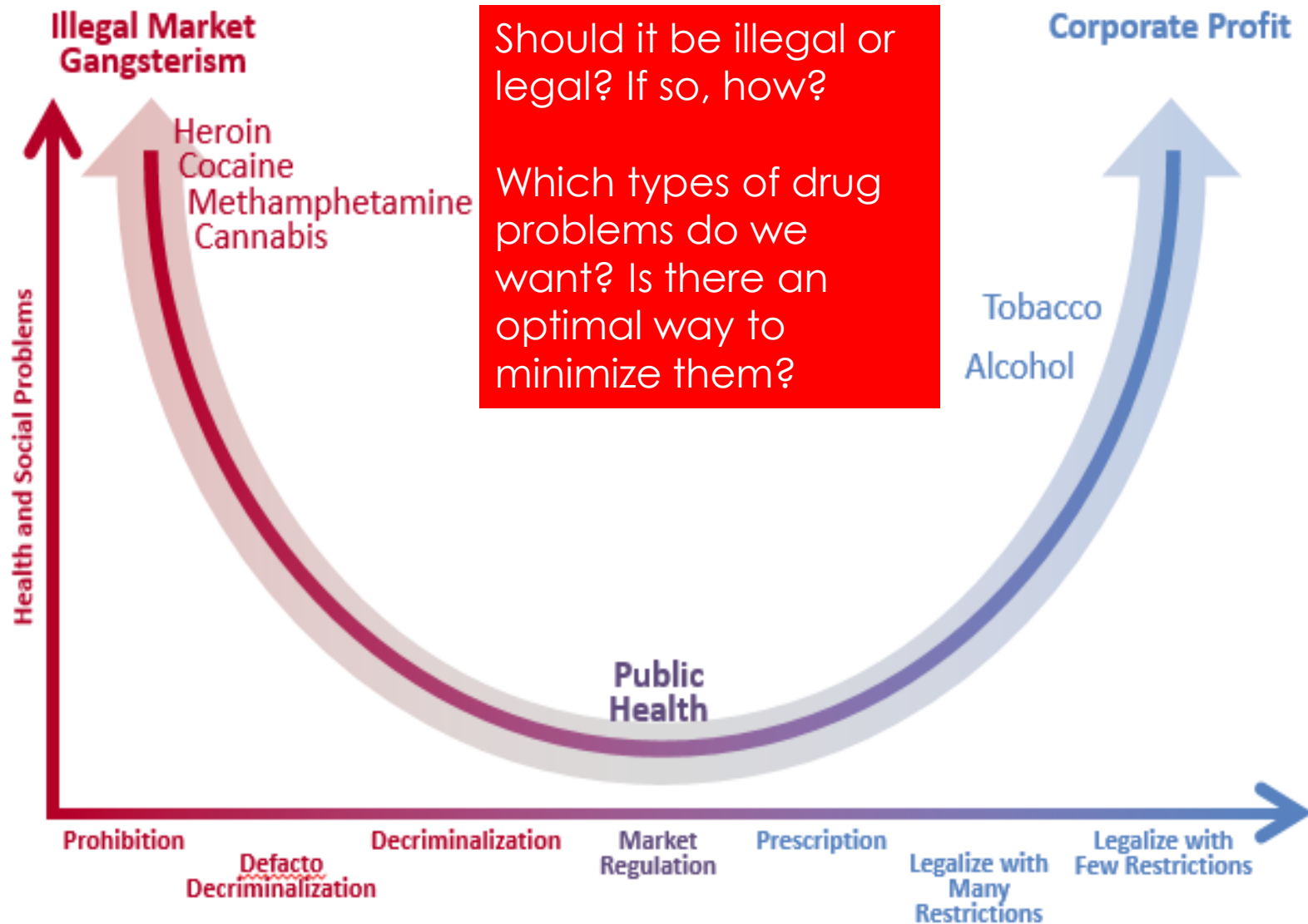


\*Denotes all types and preparations

# Degree of Problems Associated with Various Policy Approaches to Addressing the Drug Problem

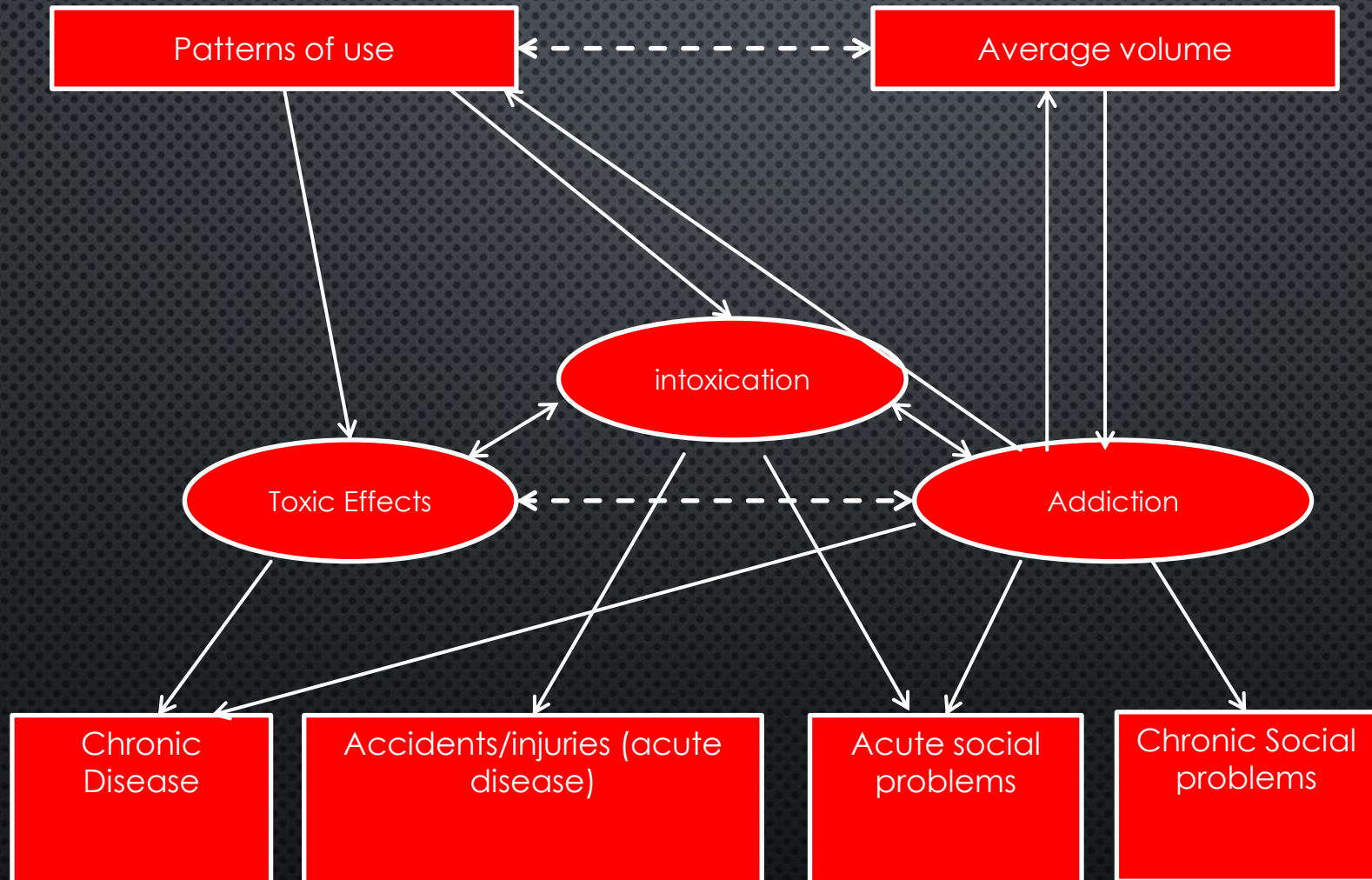


# Degree of Problems Associated with Various Policy Approaches to Addressing the Drug Problem



# HOW COULD INCREASED USE OF MJ CAUSE HARM TO PUBLIC HEALTH AND PUBLIC SAFETY?

## Toxicity, Intoxication, and Addiction



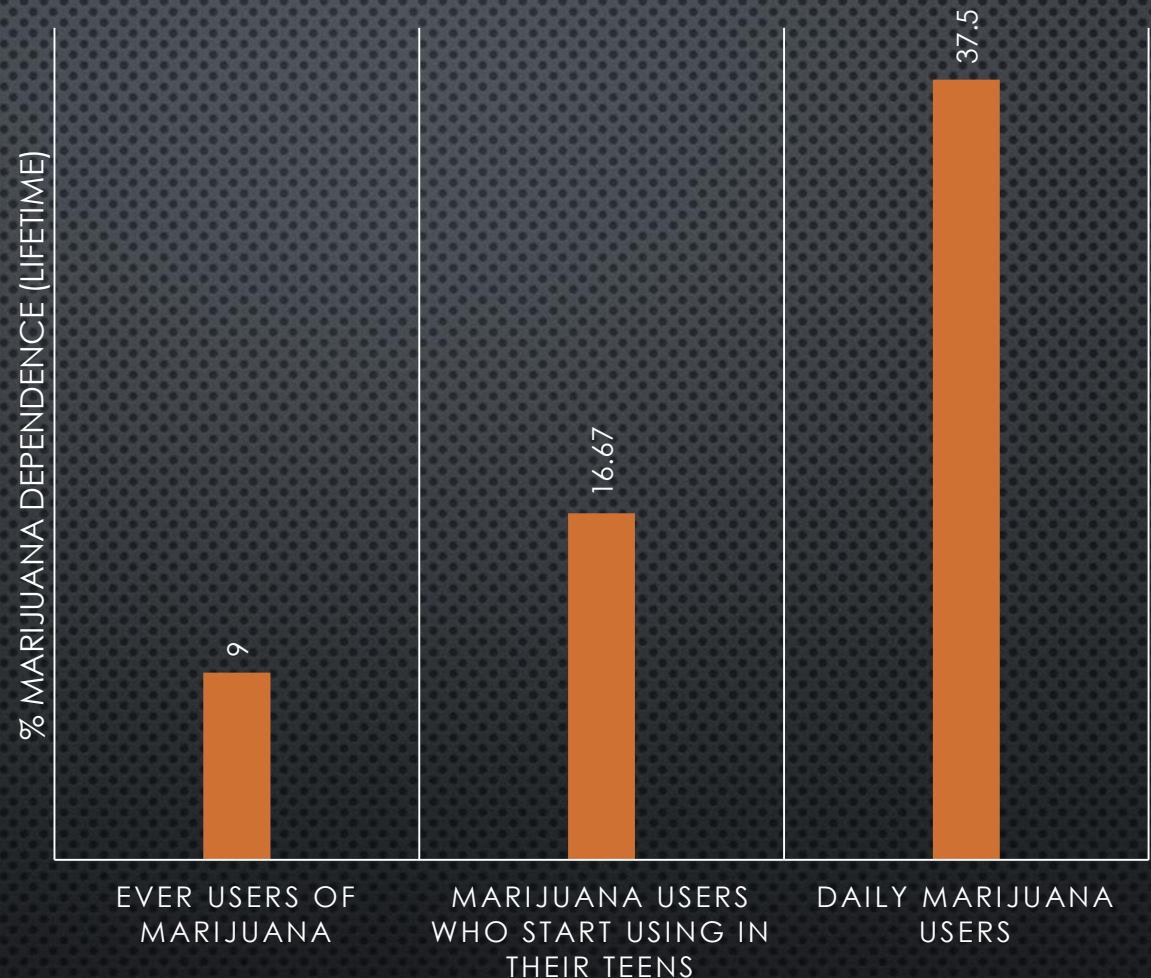


Addiction

# ADDICTIVENESS OF MARIJUANA

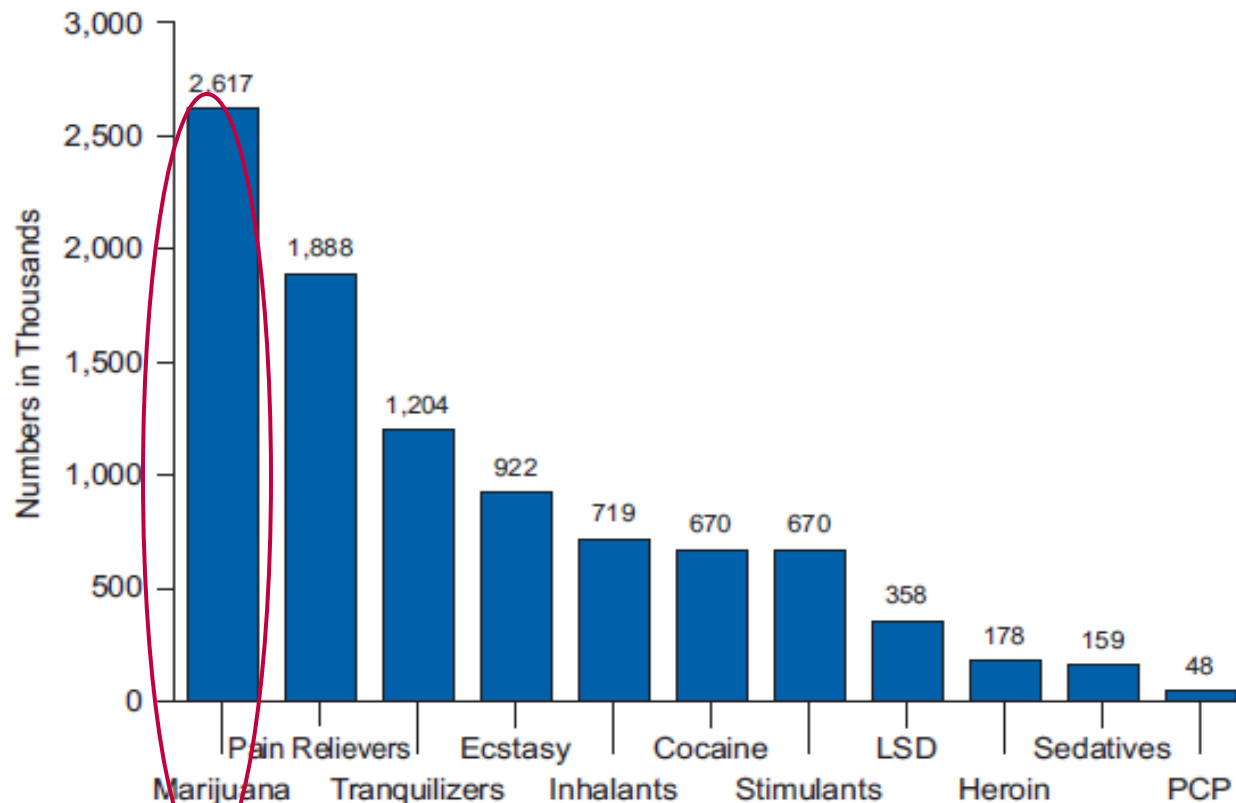
“ADOLESCENTS, ESPECIALLY TROUBLED ONES, AND PEOPLE WITH PSYCHIATRIC DISORDERS (INCLUDING SUBSTANCE ABUSE) APPEAR MORE LIKELY THAN THE GENERAL POPULATION TO BECOME DEPENDENT ON MARIJUANA...”

-- INSTITUTE OF MEDICINE



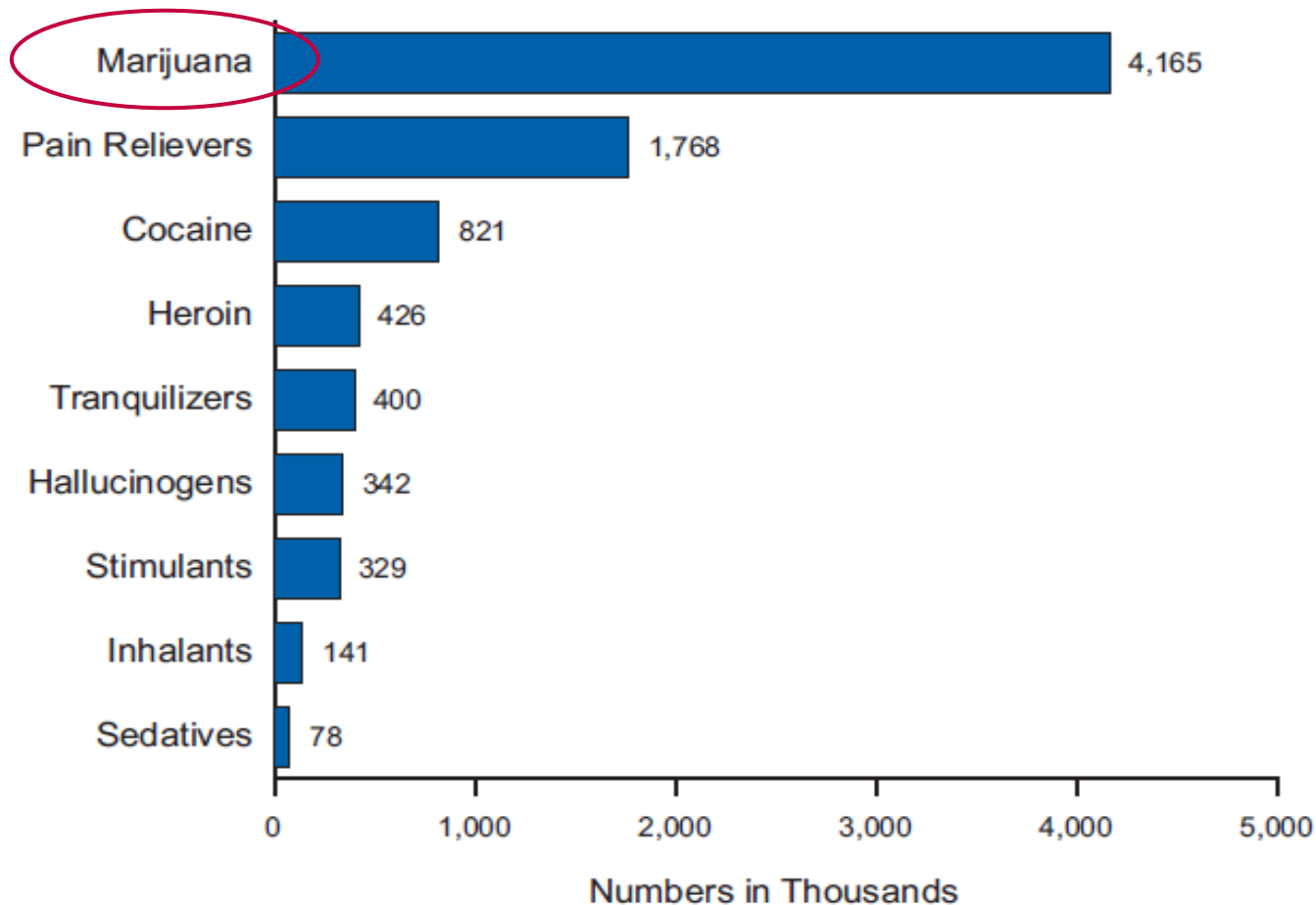
Anthony, J.; Warner, L.A.; and Kessler, R.C. *Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey*. *Exp Clin Psychopharmacol* 2:244–268, 1994;  
Hall, W.; and Degenhardt, L. *Adverse health effects of non-medical cannabis use*. *Lancet* 374:1383–1391, 2009;  
Hall, W. *The adverse health effects of cannabis use: What are they, and what are their implications for policy?* *Int J of Drug Policy* 20:458–466, 2009

## PAST YEAR INITIATES OF SPECIFIC DRUGS UNITED STATES

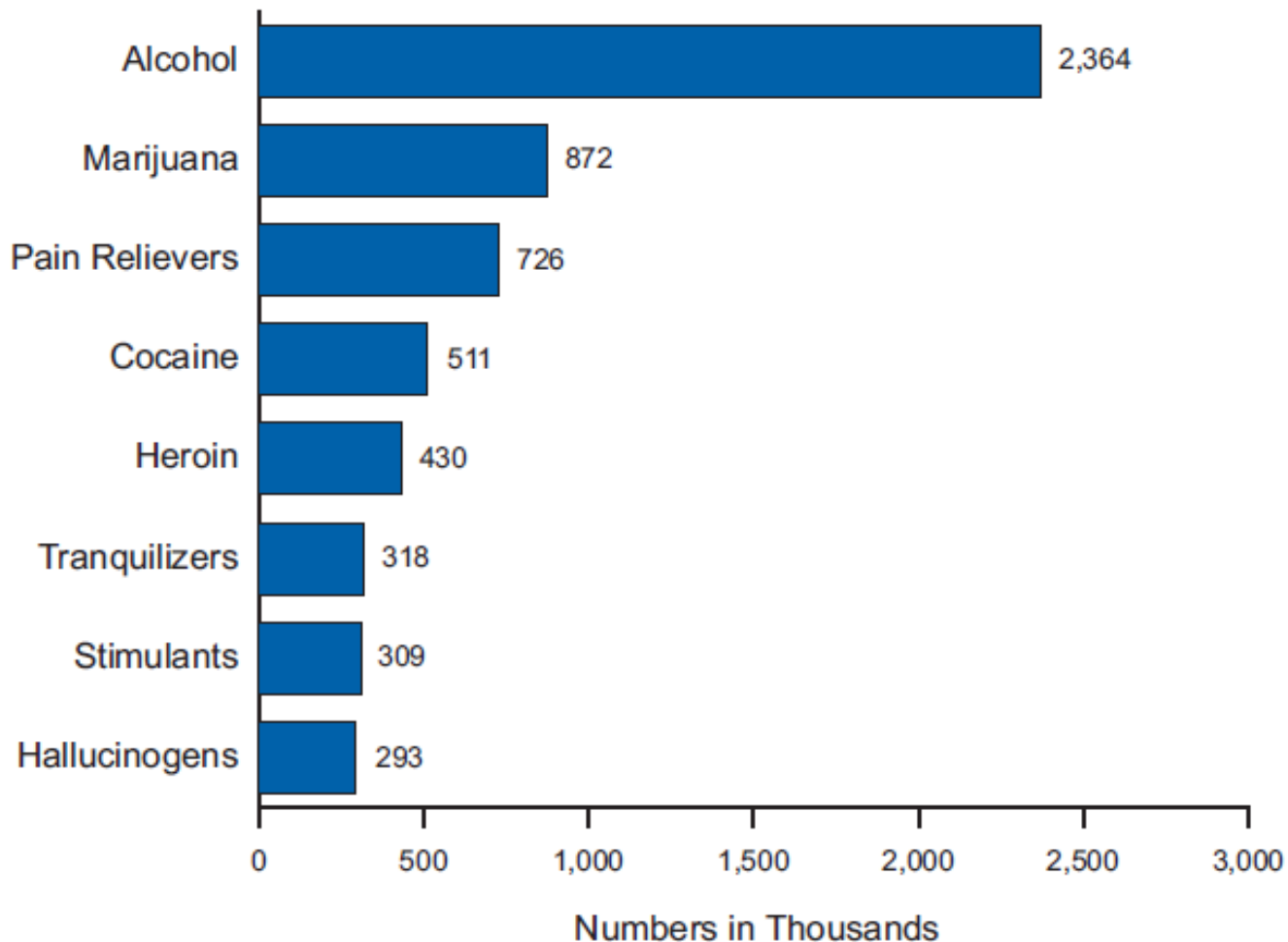


Note: Numbers refer to persons who used a specific drug for the first time in the past year, regardless of whether initiation of other drug use occurred prior to the past year.

Other than alcohol, MJ is the common drug for which most Americans Meet criteria for substance use disorder



Other than alcohol, MJ is the common drug for which most Americans seek SUD treatment



# Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013

Deborah S. Hasin, PhD; Tulshi D. Saha, PhD; Bradley T. Kerridge, PhD; Risë B. Goldstein, PhD, MPH;  
S. Patricia Chou, PhD; Haitao Zhang, PhD; Jeeseun Jung, PhD; Roger P. Pickering, MS; W. June Ruan, MA;  
Sharon M. Smith, PhD; Boji Huang, MD, PhD; Bridget F. Grant, PhD, PhD

**IMPORTANCE** Laws and attitudes toward marijuana in the United States are becoming more permissive but little is known about whether the prevalence rates of marijuana use and marijuana use disorders have changed in the 21st century.

**OBJECTIVE** To present nationally representative information on the past-year prevalence rates of marijuana use, marijuana use disorder, and marijuana use disorder among marijuana users in the US adult general population and whether this has changed between 2001-2002 and 2012-2013.

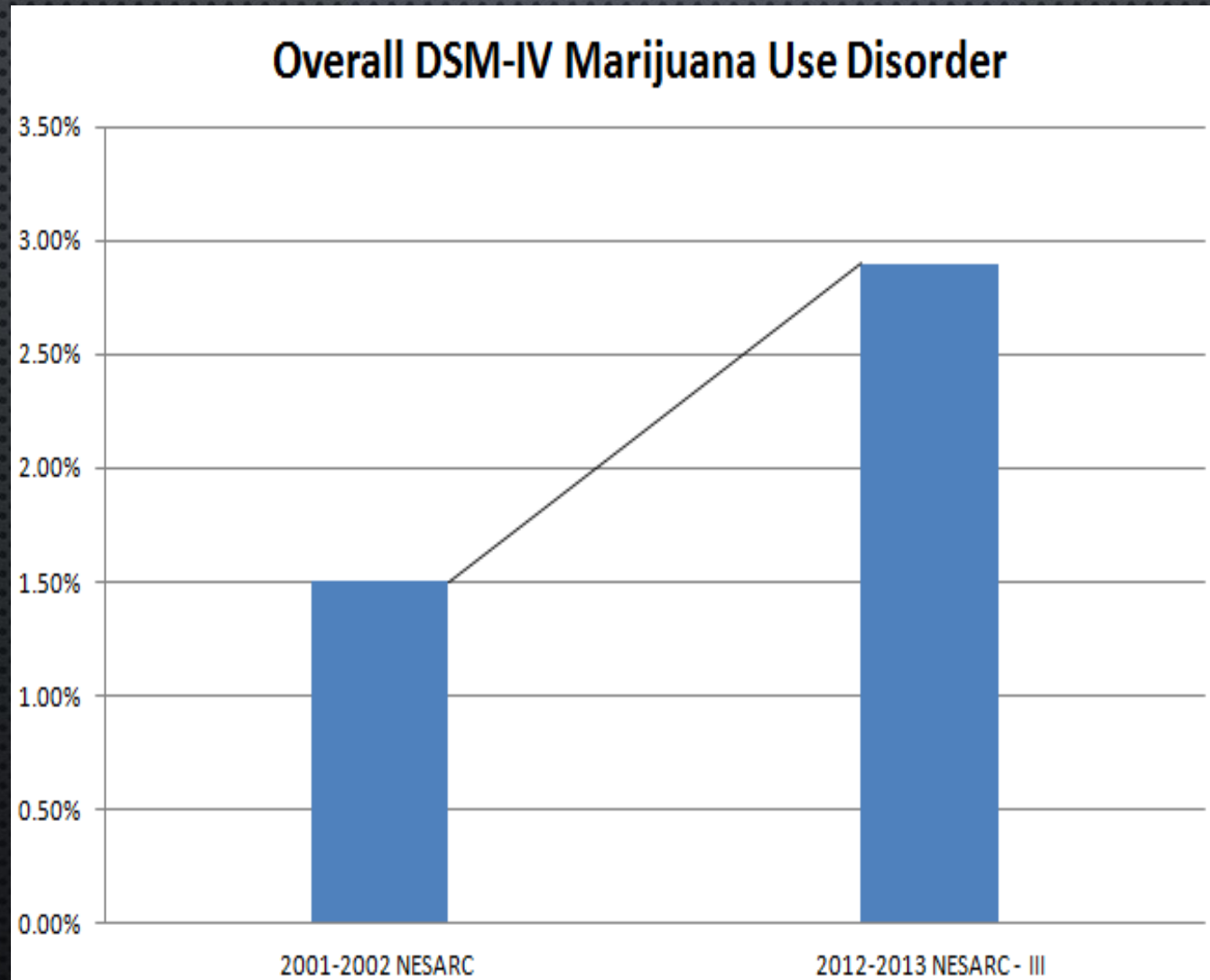
**DESIGN, SETTING, AND PARTICIPANTS** Face-to-face interviews conducted in surveys of 2 nationally representative samples of US adults: the National Epidemiologic Survey on Alcohol and Related Conditions (data collected April 2001-April 2002; N = 43 093) and the National Epidemiologic Survey on Alcohol and Related Conditions-III (data collected April 2012-June 2013; N = 36 309). Data were analyzed March through May 2015.


**MAIN OUTCOMES AND MEASURES** Past-year marijuana use and *DSM-IV* marijuana use disorder (abuse or dependence).

**RESULTS** The past-year prevalence of marijuana use was 4.1% (SE, 0.15) in 2001-2002 and 9.5% (SE, 0.27) in 2012-2013, a significant increase ( $P < .05$ ). Significant increases were also found across demographic subgroups (sex, age, race/ethnicity, education, marital status, income, urban/rural, and region). The past-year prevalence of *DSM-IV* marijuana use disorder was 1.5% (0.08) in 2001-2002 and 2.9% (SE, 0.13) in 2012-2013 ( $P < .05$ ). With few exceptions, increases in the prevalence of marijuana use disorder between 2001-2002 and 2012-2013 were also statistically significant ( $P < .05$ ) across demographic subgroups. However, the prevalence of marijuana use disorder among marijuana users decreased significantly from 2001-2002 (35.6%; SE, 1.37) to 2012-2013 (30.6%; SE, 1.04).

**CONCLUSIONS AND RELEVANCE** The prevalence of marijuana use more than doubled between 2001-2002 and 2012-2013, and there was a large increase in marijuana use disorders during that time. While not all marijuana users experience problems, nearly 3 of 10 marijuana users manifested a marijuana use disorder in 2012-2013. Because the risk for marijuana use disorder did not increase among users, the increase in prevalence of marijuana use disorder is owing to an increase in prevalence of users in the US adult population. Given changing laws and attitudes toward marijuana, a balanced presentation of the likelihood of adverse consequences of marijuana use to policy makers, professionals, and the public is needed.

# PAST YEAR *DSM-IV* MARIJUANA USE DISORDER





Toxic  
Effects



# Residual Effects of Cannabis Use on Neurocognitive Performance Prolonged Abstinence: A Meta-Analysis

Amy M. Schreiner and Michael E. Dunn  
University of Central Florida

## 1. First Analysis (k=33)

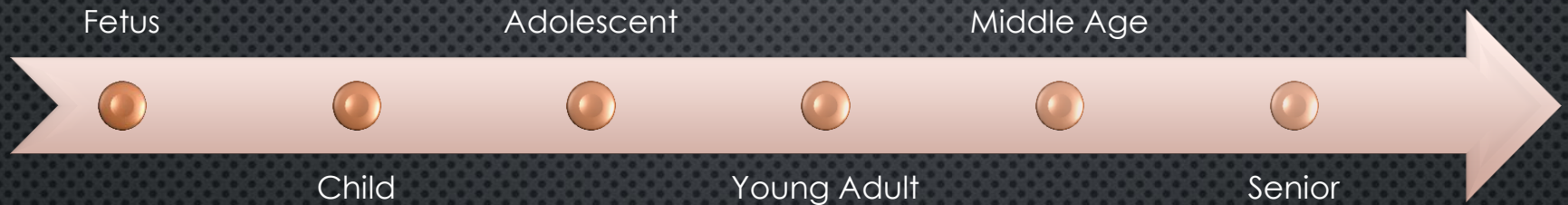
Results: Neurocognitive deficits in most domains of functioning present early during abstinence

## 2. Second Sub-Analysis (k=13)

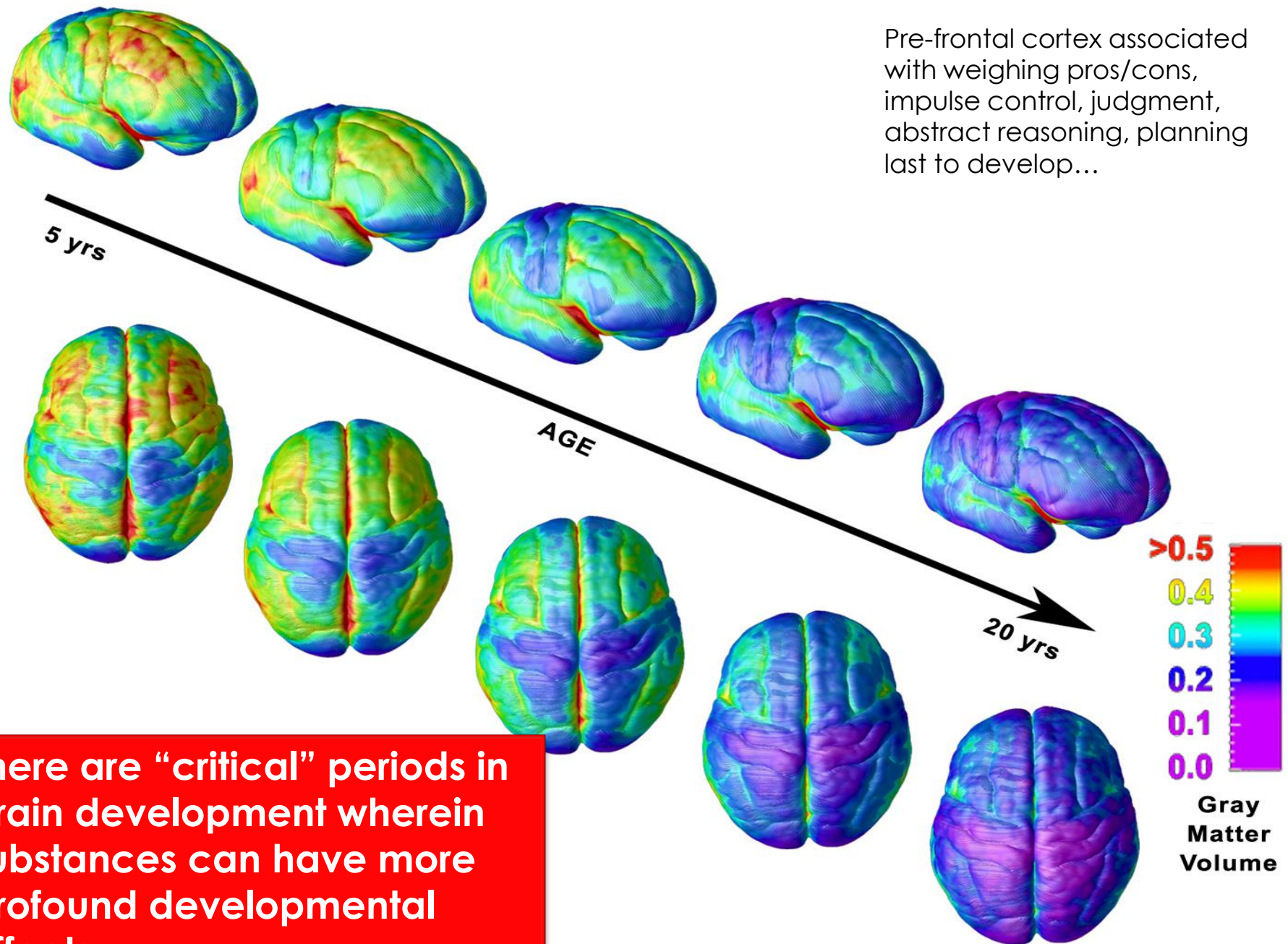
Results: Not present after 25 or more days of abstinence

3. ... but what about among youth?

# A LIFE COURSE PERSPECTIVE



The life course perspective has the advantage of recognizing developmental stages as factors facilitating or inhibiting change and continuity, and/or protective and risk factors, that may differ across the life span (Hser & Anglin, 2008).



Pre-frontal cortex associated with weighing pros/cons, impulse control, judgment, abstract reasoning, planning last to develop...

There are “critical” periods in brain development wherein substances can have more profound developmental effects...



Contents lists available at [ScienceDirect](#)

# Pharmacology & Therapeutics

journal homepage: [www.elsevier.com/locate/pharmthera](http://www.elsevier.com/locate/pharmthera)



Associate editor: S. Andersen

## Cannabis and adolescent brain development



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### ARTICLE INFO

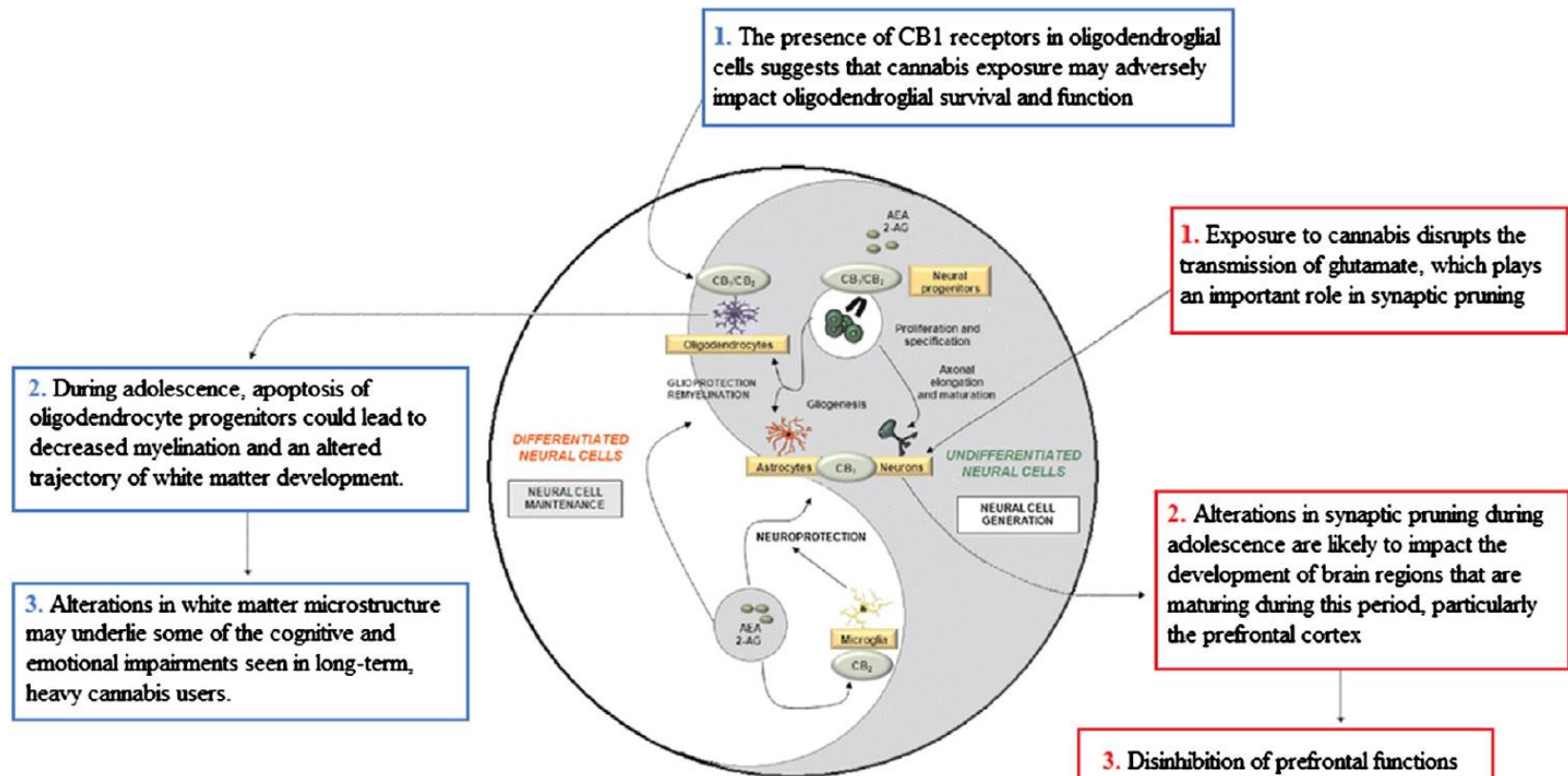
Available online 20 November 2014

#### Keywords:

Cannabis  
Adolescence  
Brain development  
Endocannabinoid  
Cognition  
Mental illness

### ABSTRACT

Heavy cannabis use has been frequently associated with increased rates of mental illness and cognitive impairment, particularly amongst adolescent users. However, the neurobiological processes that underlie these associations are still not well understood. In this review, we discuss the findings of studies examining the acute and chronic effects of cannabis use on the brain, with a particular focus on the impact of commencing use during adolescence. Accumulating evidence from both animal and human studies suggests that regular heavy use during this period is associated with more severe and persistent negative outcomes than use during adulthood, suggesting that the adolescent brain may be particularly vulnerable to the effects of cannabis exposure. As the endocannabinoid system plays an important role in brain development, it is plausible that prolonged use during adolescence results in a disruption in the normative neuromaturational processes that occur during this period. We identify synaptic pruning and white matter development as two processes that may be adversely impacted by cannabis exposure during adolescence. Potentially, alterations in these processes may underlie the cognitive and emotional deficits that have been associated with regular use commencing during adolescence.



MJ use during adolescence may affect neuromaturation processes through two pathways:

**1. Alters synaptic pruning** (via disrupting glutamate Transmission) leading to greater disinhibition in prefrontal regions leading to psychotic symptoms

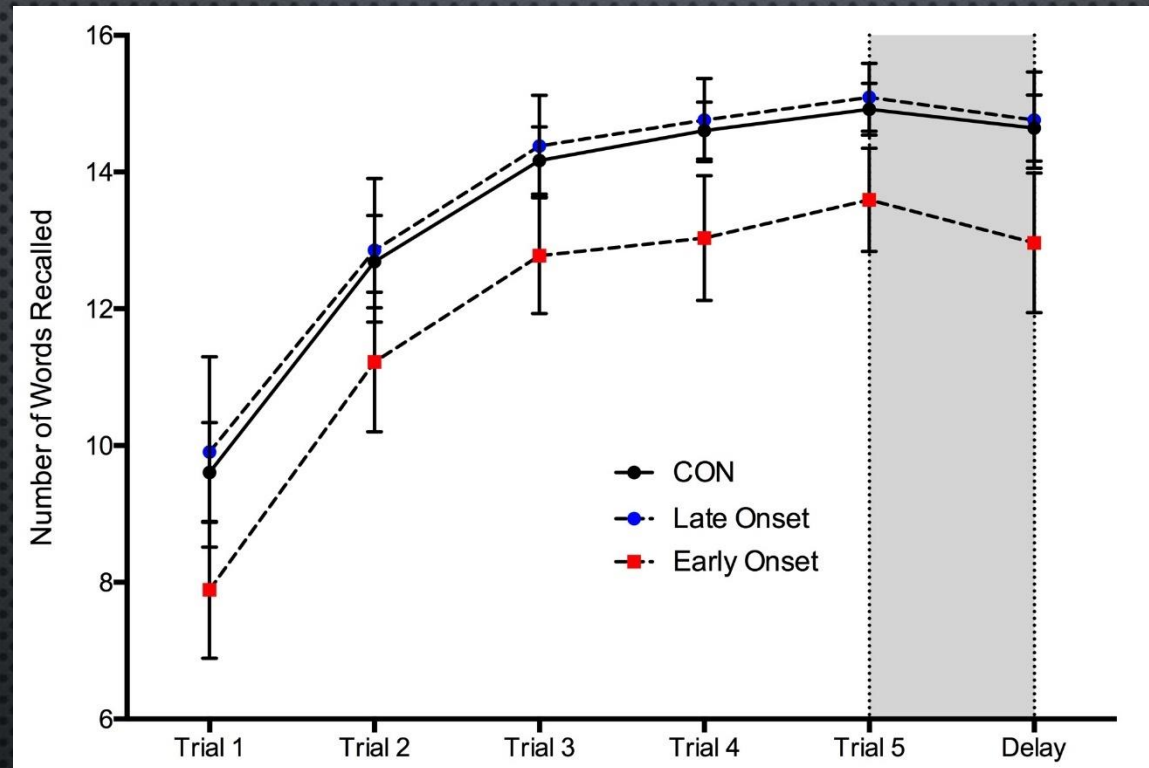
**2. Decreased myelination altering development of white matter** leading to cognitive-emotional impairments

cells during prenatal and early post-natal stages of brain development (grey/yellow side) as neuronal migration and axonal pathfinding, as well as the generation of glial cells, including functions of the endocannabinoid system and alter brain development: (i) by interfering

# IMPLICATIONS FOR LEGAL, COMMERCIALIZED RECREATIONAL USE

- IMPORTANT IMPLICATIONS BECAUSE CO, WHICH HAS A LEGAL AGE OF USE SET AT 21 YRS OR OLDER, JUST RELEASED LATEST REPORT ON MJ IMPACT AND FOUND THAT WHILE MJ USE NATIONALLY DECLINED 4% IN 2015 AMONG YOUTH, IT WENT UP 20% IN CO DURING THE PAST 2 YRS IN WHICH MJ USE WAS LEGALIZED

# Potential impact on academic achievement: Marijuana Users Show Worse Performance on a Memory Test



- **Early onset MJ users (<16), show impaired learning compared to non-users**
- **Could mean students using MJ regularly could have difficulty attending to and learning new information**

# Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier<sup>a,b,1</sup>, Avshalom Caspi<sup>a,b,c,d,e</sup>, Antony Ambler<sup>e,f</sup>, HonaLee Harrington<sup>b,c,d</sup>, Renate Houts<sup>b,c,d</sup>, Richard S. E. Keefe<sup>d</sup>, Kay McDonald<sup>f</sup>, Aimee Ward<sup>f</sup>, Richie Poulton<sup>f</sup>, and Terrie E. Moffitt<sup>a,b,c,d,e</sup>

<sup>a</sup>Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, <sup>b</sup>Department of Psychology and Neuroscience, and <sup>c</sup>Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; <sup>d</sup>Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; <sup>e</sup>Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and <sup>f</sup>Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

**Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants**

**neuropsychological test performance after a period of abstinence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is re-**

Even when recent MJ use was taken into account along with other confounds heavy use during teen years was associated with an 8 point drop in IQ

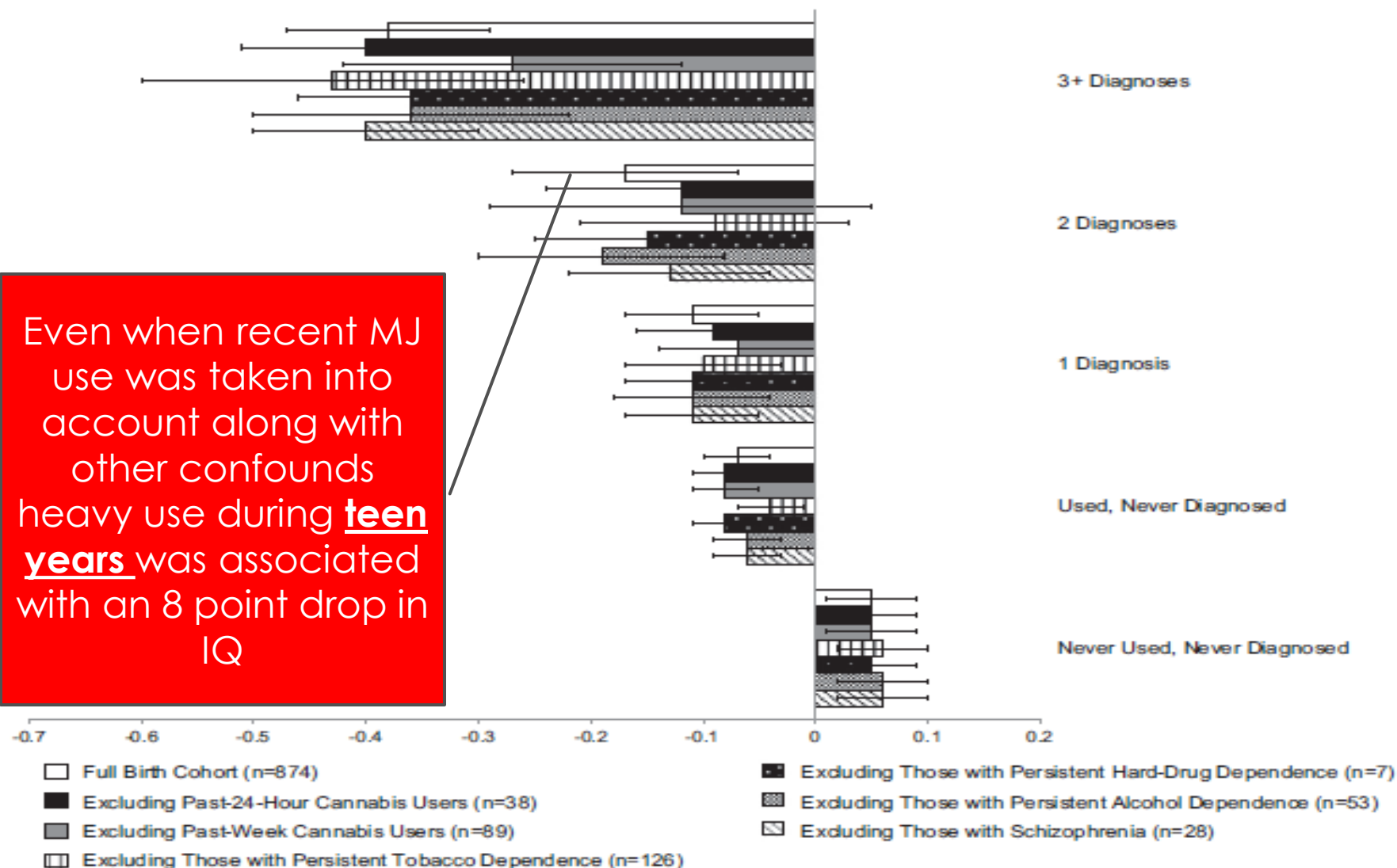


Fig. 1. Ruling out alternative explanations. Shown is change in full-scale IQ (n SD units) from childhood to adulthood as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. Change scores are presented for the full birth cohort and the cohort excluding (i) past 24-h cannabis users, (ii) past-week cannabis users, (iii) those with persistent tobacco dependence, (iv) those with persistent hard-drug dependence, (v) those with persistent alcohol dependence, and (vi) those with lifetime schizophrenia. Persistent tobacco, hard-drug, and alcohol dependence were each defined as dependence at three or more study waves. IQ decline could not be explained by other factors. Error bars = SEs.

sizes, representing within-person IQ change as a function of tobacco, hard-drug, or alcohol dependence), and schizophrenia

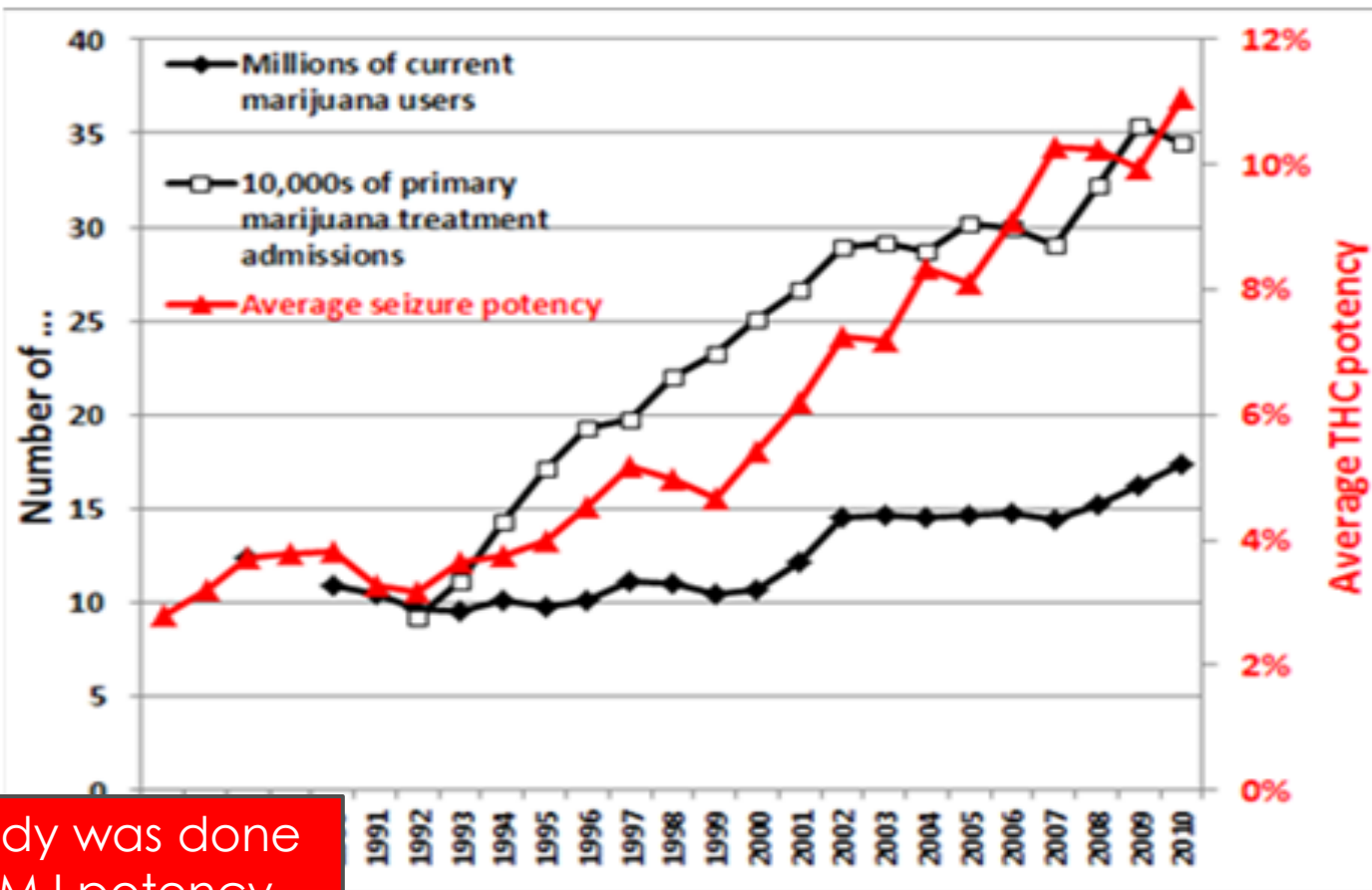
# FIVE OUTCOMES FROM THE LONGITUDINAL MEIER ET AL (2012) STUDY

USING PROSPECTIVE DESIGN OVER 20 YEARS ASSESSING NEUROPSYCHOLOGICAL FUNCTIONING USING VALIDATED TESTS (WHICH IF ANYTHING WOULD BE EXPECTED TO GO UP DUE TO PRACTICE EFFECTS):

- 1. FINDINGS NOT DUE TO PREMORBID NEUROPSYCHOLOGICAL DEFICITS
- 2. IMPAIRMENT WAS GLOBAL AND DETECTABLE ACROSS 5 DOMAINS OF NEUROPSYCHOLOGICAL FUNCTIONING. STILL PRESENT AFTER OTHER DRUG USE ACCOUNTED FOR
- 3. NEUROPSYCHOLOGICAL DECLINE DID NOT OCCUR SOLELY BECAUSE MJ USERS HAD LESS EDUCATION.
- 4. IMPAIRMENT WAS APPARENT TO THIRD-PARTY INFORMANTS AND PERSISTENT MJ USE INTERFERED WITH EVERYDAY COGNITIVE FUNCTIONING.
- 5. AMONG ADOLESCENT ONSET FORMER PERSISTENT MJ USERS, IMPAIRMENT WAS STILL EVIDENT AFTER CESSATION OF USE FOR 1 Y OR MORE.
- COLLECTIVELY, FINDINGS CONSISTENT WITH SPECULATION THAT CANNABIS USE IN ADOLESCENCE, WHEN THE BRAIN IS UNDERGOING CRITICAL DEVELOPMENT, MAY HAVE NEUROTOXIC EFFECTS.

What will be the effects of higher potency MJ?

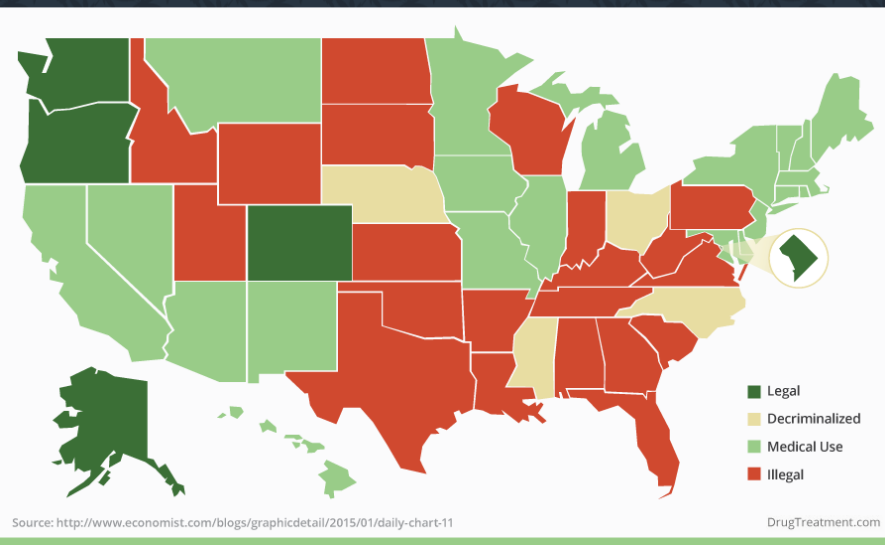
***MARIJUANA USERS, TREATMENT ADMISSIONS, AND AVERAGE POTENCY:  
1986-2010***



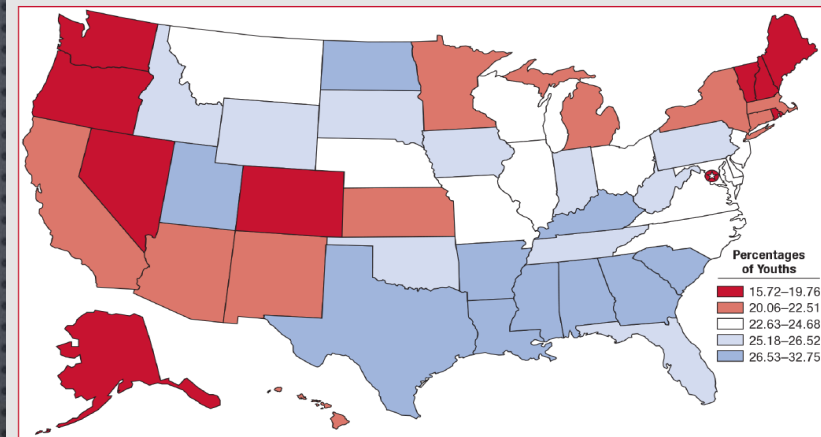
Sources: [NSDUH](#), [TEDS](#), National Seizure System

That study was done  
when MJ potency  
was lower....  
Increased potency in  
past 20 years

# Legality of Marijuana in the United States

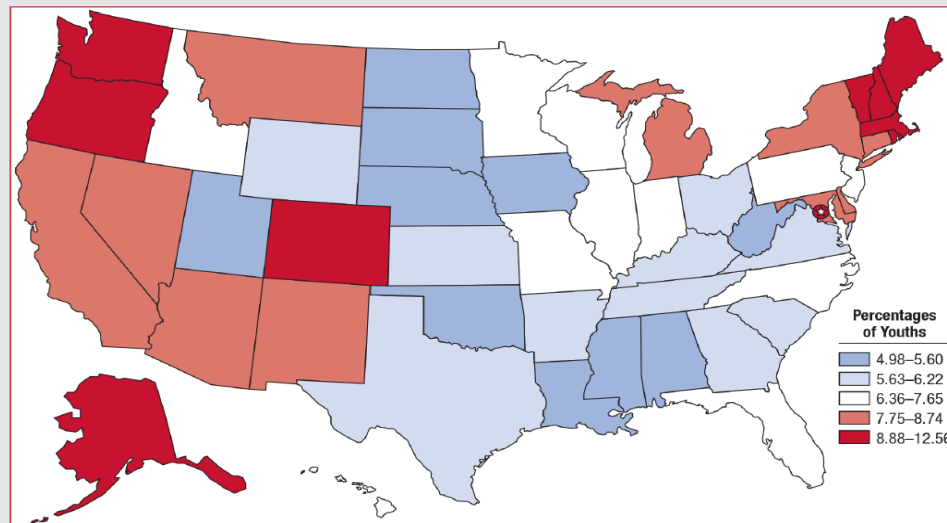


**Figure 2. Perceptions of great risk of harm from smoking marijuana once a month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014**



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2013 and 2014.

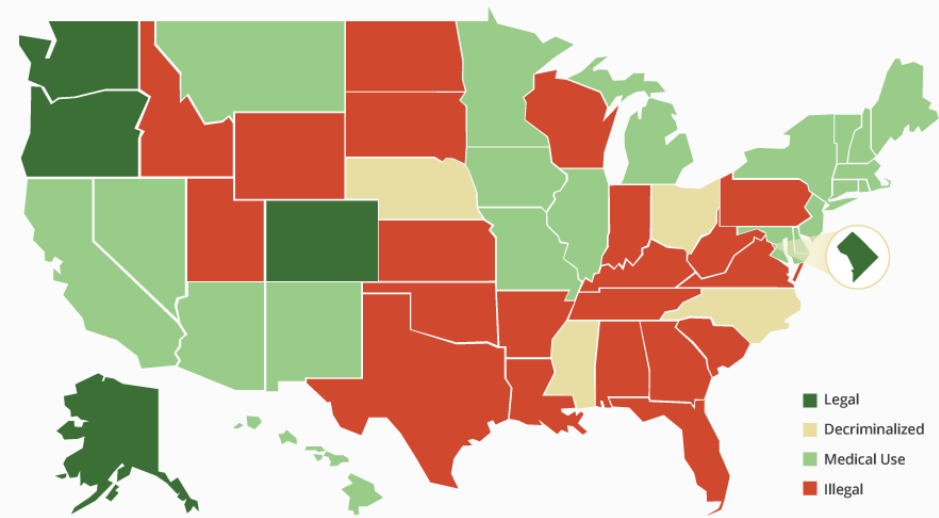
**Figure 1. Marijuana use in the past month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014**



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2013 and 2014.

Will legalization lead to Increased consumption of MJ?

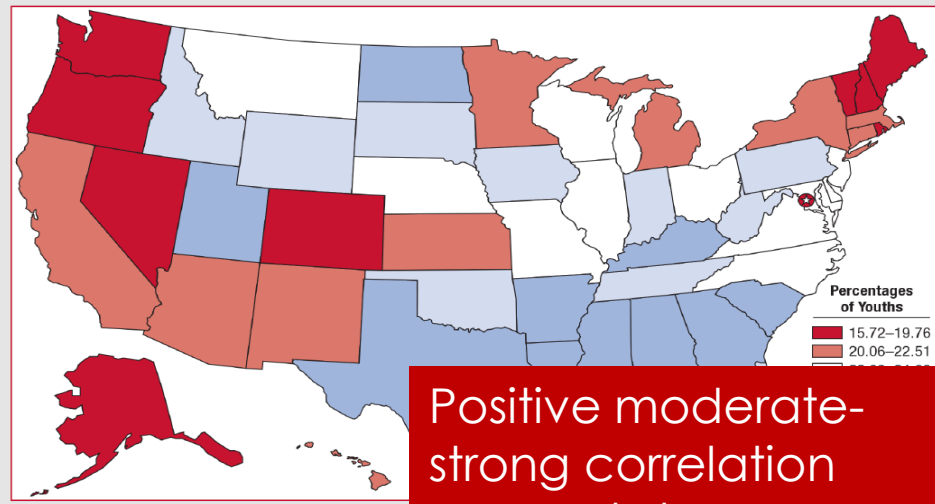
# Legality of Marijuana in the United States



Source: <http://www.economist.com/blogs/graphicdetail/2015/01/daily-chart-11>

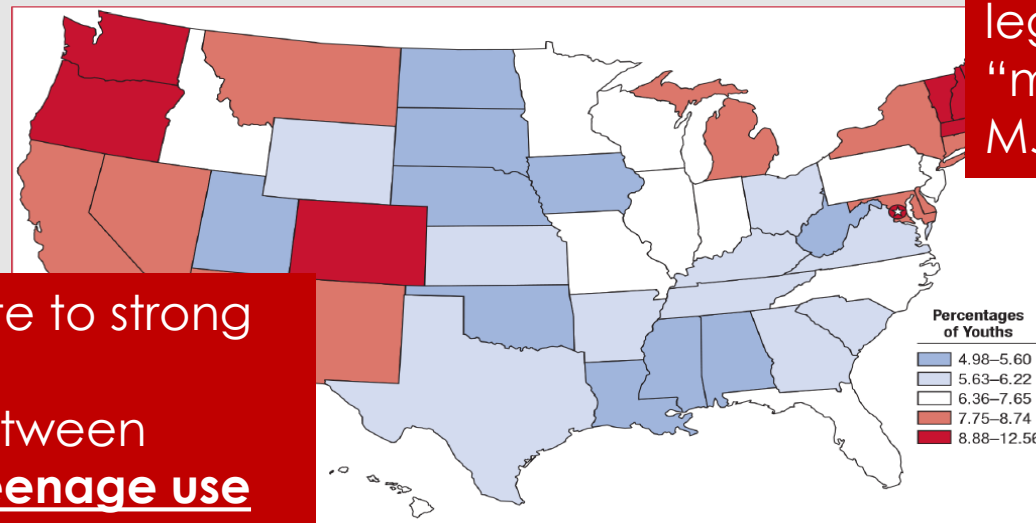
DrugTreatment.com

Figure 2. Perceptions of great risk of harm from smoking marijuana once a month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014



Source: SAMHSA, Center for Behavior

Figure 1. Marijuana use in the past month among youths aged 12 to 17 state: percentages, annual averages, 2013-2014



For Behavioral Health Statistics and Quality, National Surveys (NSDUHs), 2013 and 2014.

Positive moderate-strong correlation across states, between less perceived harm and legalization and “medicalization” of MJ

Positive moderate to strong correlation across states, between higher rates of teenage use and legalization and “medicalization” of MJ

# IMPACT OF EDIBLES?



## Kids and Marijuana Edibles: A Worrisome Trend Emerges

Experts say states should mandate child-resistant packaging.

**E**Ds are seeing a surge in the number of young children having adverse reactions to marijuana. In three-quarters of the cases reported from 2000 through 2013, the children were younger than three years old, ages when children tend to explore their environment by mouth. Most children ate items found in their homes, such as brownies, cookies, candy, and other foods spiked with marijuana.

“A typical adult serving size for a marijuana edible often is a quarter of a brownie, but a small child eats an entire brownie and ends up in the [ED],” says Sarah Ramsay, nurse manager at the Rocky Mountain Poison and Drug Center in Denver.

Data from the National Poison Data System show that the rate of marijuana exposure among children younger than six in the United States rose 147.5% from 2006 to 2013, particularly in states where medical marijuana use is legal.

From 2000 to 2013, poison control centers received reports on 1,969 children younger than six who were exposed to marijuana. Boys and girls were affected equally. Almost half (48%) of ex-



Photo by Jeff Chiu / Associated Press.

high concentrations of the drug's \_\_\_\_\_ give a marijuana edible to a child

NATIONAL POISONING SYSTEM  
DATA SHOW THAT MJ  
EXPOSURE AMONG KIDS <6YRS  
ROSE 148% FROM 2006-  
2013, PARTICULARLY IN STATES  
WHERE MED MJ IS LEGAL

# Pediatric Marijuana Exposures in a Medical Marijuana State

George Sam Wang, MD; Genie Roosevelt, MD, MPH; Kennon Heard, MD

← Editorial pages 600 and 602

**IMPORTANCE** An increasing number of states are decriminalizing the use of medical marijuana, and the effect on the pediatric population has not been evaluated.

**OBJECTIVE** To compare the proportion of marijuana ingestions by young children who sought care at a children's hospital in Colorado before and after modification of drug enforcement laws in October 2009 regarding medical marijuana possession.

**DESIGN** Retrospective cohort study from January 1, 2005, through December 31, 2011.

**SETTING** Tertiary-care children's hospital emergency department in Colorado.

**PARTICIPANTS** A total of 1378 patients younger than 12 years evaluated for unintentional ingestions: 790 patients before September 30, 2009, and 588 patients after October 1, 2009.

**MAIN EXPOSURE** Marijuana ingestion.

**MAIN OUTCOMES AND MEASURES** Marijuana exposure visits, marijuana source, symptoms, and patient disposition.

**RESULTS** The proportion of ingestion visits in patients younger than 12 years (age range, 8 months to 12 years) that were related to marijuana exposure increased after September 30, 2009, from 0 of 790 (0%; 95% CI, 0%-0.6%) to 14 of 588 (2.4%; 95% CI, 1.4%-4.0%) ( $P < .001$ ). Nine patients had lethargy, 1 had ataxia, and 1 had respiratory insufficiency. Eight patients were admitted, 2 to the intensive care unit. Eight of the 14 cases involved medical marijuana, and 7 of these exposures were from food products.

**CONCLUSIONS AND RELEVANCE** We found a new appearance of unintentional marijuana ingestions by young children after modification of drug enforcement laws for marijuana possession in Colorado. The consequences of unintentional marijuana exposure in children should be part of the ongoing debate on legalizing marijuana.

*JAMA Pediatr.* 2013;167(7):630-633. doi:10.1001/jamapediatrics.2013.140  
Published online May 27, 2013.

**Author Affiliations:** Rocky Mountain Poison and Drug Center, Denver Health, Denver, Colorado (Wang, Heard); Department of Pediatrics, Section of Emergency Medicine, University of Colorado School of Medicine, Aurora (Roosevelt).

**Corresponding Author:** George Sam Wang, MD, Rocky Mountain Poison and Drug Center, 777 Bannock St, Office Box 0180, Denver, CO 80204 (george.wang@childrenscolorado.org).

**Table 1. Demographics of Patients Seen in the Children's Hospital Emergency Department for Ingestions<sup>a</sup>**

| Characteristic       | January 1, 2005,<br>Through September 30,<br>2009 | October 1, 2009,<br>Through December 31,<br>2011 |
|----------------------|---|--|
| No. of patients      | 790   | 588  |
| Age, median (IQR), y | 2.6 (1.6-3.0)                                     | 2.3 (1.5-3.6)                                    |
| Male sex             | 449 (56.8)  | 334 (56.8)                                       |
| Types of ingestions  |   |  |
| Acetaminophen        | 90 (11.3)   | 48 (8.2)   |
| Antihistamine        | 43 (5.4)  | 32 (5.4)   |
| Antidepressant       | 23 (2.9)  | 14 (2.3)   |
| Antitussive          | 18 (2.2)  | 14 (2.3)   |
| Marijuana exposures  | 0   | 14 (2.3)   |

New increase in unintentional marijuana ingestions by young children (e) unless otherwise noted.

Opposite trend to all other toxic ingestions

## Impact of Marijuana on Response Inhibition: An fMRI Study in Young Adults

Andra M. Smith<sup>1\*</sup>, Rocio A. López Zunini<sup>1</sup>, Christopher D. Anderson<sup>1</sup>, Carmelinda A. Longo<sup>1</sup>,

Ian Cameron<sup>2</sup>, Matthew J. Hogan<sup>3</sup>, Peter A. Fried<sup>3</sup>

<sup>1</sup>School of Psychology, University of Ottawa, Ottawa, Canada

<sup>2</sup>The Ottawa Hospital, Department of Diagnostic Imaging, Ottawa, Canada

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Received June 26, 2011; revised July 19, 2011; accepted August 4, 2011

### Abstract

**Rationale:** Marijuana use in adolescence is prevalent and increasing. Understanding the neural correlates of the impact of this use is critical for policy making and for youth awareness. **Objectives:** The effects of marijuana use on response inhibition were investigated in 19 - 21-year-olds using functional magnetic resonance imaging (fMRI). **Methods:** Participants were members of the Ottawa Prenatal Prospective Study, a longitudinal study that collected a unique body of information on participants from infancy to young adulthood including: prenatal drug history, detailed cognitive/behavioral performance, and current and past drug use. This information allowed for the control of an unparalleled number of potentially confounding variables including: prenatal marijuana, nicotine, alcohol, and caffeine exposure and offspring alcohol, marijuana, and nicotine use. Ten marijuana users and 14 nonusers that served as controls performed a Go/No-Go task while fMRI blood oxygen level-dependent response was examined. **Results:** Despite similar task performance, there was a positive relationship between amount of marijuana smoked and activation in right thalamus, premotor cortex and middle frontal gyrus. These regions form part of the neural network responsible for inhibition control. There was also a positive dose dependent relationship with marijuana and activation in inferior parietal lobe and precuneus, also parts of response inhibition pathways. **Conclusions:** These results suggest a dose dependent alteration in neural functioning during response inhibition after controlling for other prenatal and current drug use. These alterations may be necessary in order to compensate for neural changes in response inhibition circuits caused by long term marijuana use that began during adolescence/young adulthood.

**Keywords:** Prefrontal Cortex, fMRI, Marijuana, Young Adulthood, Response Inhibition

### 1. Introduction

Research has demonstrated that the inability to successfully monitor and inhibit inappropriate behaviours is apparent in substance abusers as well as in other individuals with altered frontal neural circuitry [1]. Such disruption in executive functioning, which can also include selective attention and short term storage of information, initiation of response to relevant information and self-monitoring of performance in order to achieve a desired goal [1], can cause severe disruption in daily life. Of these elements, however, response inhibition is most vital since it allows for successful adaptation to the environment,

recognizing unexpected situations, making plans and changing behaviour accordingly.

Functional magnetic resonance imaging (fMRI) research has shown that response inhibition is mediated by a wide neural network that involves the frontal lobes as well as circuits connecting the frontal lobes with other regions such as the parietal lobes, cerebellum, striatum and thalamus [2-3]. Other observed regions include the premotor area, the supplementary motor area, the dorso-lateral and orbitofrontal areas and the anterior cingulate cortex [4].

The 2011 Monitoring the Future Survey reported that there is an increase in American youth marijuana use and

## Effects of marijuana on visuospatial working memory: an fMRI study in young adults

Andra M. Smith · Carmelinda A. Longo ·

Peter A. Fried · Matthew J. Hogan · Ian Cameron

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### Abstract

**Objectives** The effects of marijuana use on visuospatial working memory were investigated in 19–21-year-olds using functional magnetic resonance imaging (fMRI).

**Methods** Participants were members of the Ottawa Prenatal Prospective Study, a longitudinal study that collected a unique body of information on participants from infancy to young adulthood including: prenatal drug history, detailed cognitive/behavioral performance, and current and past drug use. This information allowed for the measurement of an unprecedented number of potentially confounding drug exposure variables including: prenatal marijuana, nicotine, alcohol, and caffeine exposure and offspring alcohol, marijuana, and nicotine use. Ten marijuana users and 14 nonusing controls performed a visuospatial 2-back task while fMRI blood oxygen level-dependent response was examined.

**Results** Despite similar task performance, marijuana users had significantly greater activation in the inferior and middle frontal gyri, regions of the brain normally associated with visuospatial working memory. Marijuana users also

had greater activation in the right superior temporal gyrus, a region of the brain not typically associated with visuospatial working memory tasks.

**Conclusions** These results suggest that marijuana use leads to altered neural functioning during visuospatial working memory after controlling for other prenatal and current drug use. This alteration appears to be compensated for by the recruitment of blood flow in additional brain regions. It is possible that this compensation may not be sufficient in more real-life situations where this type of processing is required and thus deficits may be observed. Awareness of these neural physiological effects of marijuana in youth is critical.

**Keywords** Visuospatial working memory · Marijuana · Executive functioning · Functional magnetic resonance imaging

### Introduction

Marijuana continues to be the most commonly used illegal drug in the world, with almost 160 million people, aged 15–64, reporting having used marijuana in the last year (World Drug Report 2007). Although the marijuana plant contains several hundred compounds, its most psychoactive ingredient is THC or delta-9-tetrahydrocannabinol (Mechoulam and Gaoni 1967). Research has found that THC binds to CB1 receptors, which are located in various concentrations throughout the brain, with high densities found in the frontal regions of the cerebral cortex and in the hippocampus (Devane et al. 1988; Herkenham et al. 1990). The frontal cortex is responsible for executive functioning processes such as decision making, planning, problem solving, focused attention, response inhibition, cognitive

Neurobiological functioning of young marijuana users on response inhibition and working memory tasks >>>

# Neurobiological functioning of young marijuana users on response inhibition and working memory tasks

- ▶ Two cross-sectional studies using fMRI from young adults in the Ottawa Prenatal Prospective Study
- ▶ 10 cannabis users and 14 non-using controls, ages 19–21
  - No differences on personality factors, psychiatric disorder (apart from CUD), SES, Conners' Parent Rating Scale of behavior.
  - Potentially meaningful differences (not statistically significant):
    - Higher verbal IQ among non-users (117 vs. 106,  $M=100$ ,  $SD=15$ )
    - Greater extraversion among non-users (59 vs. 50,  $M=50$ ,  $SD=10$ )
  - Differences on alcohol and cigarette smoking controlled for statistically
  - No other drugs of misuse, no parent DSM-IV diagnosis
- ▶ Measures:
  - Visuospatial working memory: measured by the N-Back task
  - Motor response inhibition: measured by the Go/No-Go task
  - fMRI completed while individuals performed the tasks

# Neurobiological functioning of young marijuana users on response inhibition and working memory tasks

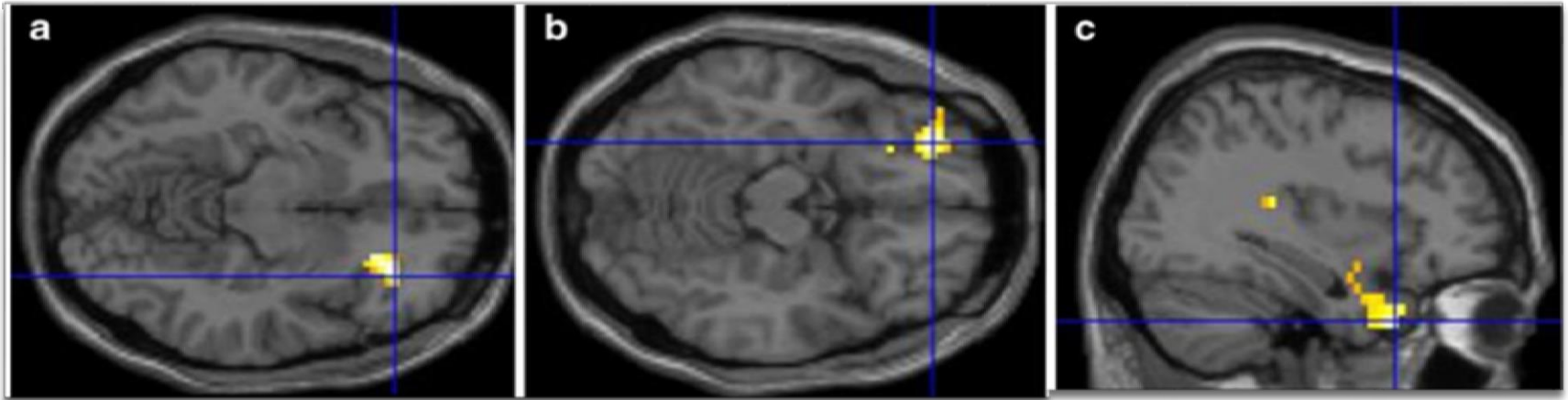
## Working Memory

- No significant differences on N-Back task
- Cannabis users: greater activation on areas of the frontal gyri indicated in visuospatial processing,
  - Brodmann areas 11 (orbitofrontal) and 38 (temporopolar)

## Response Inhibition

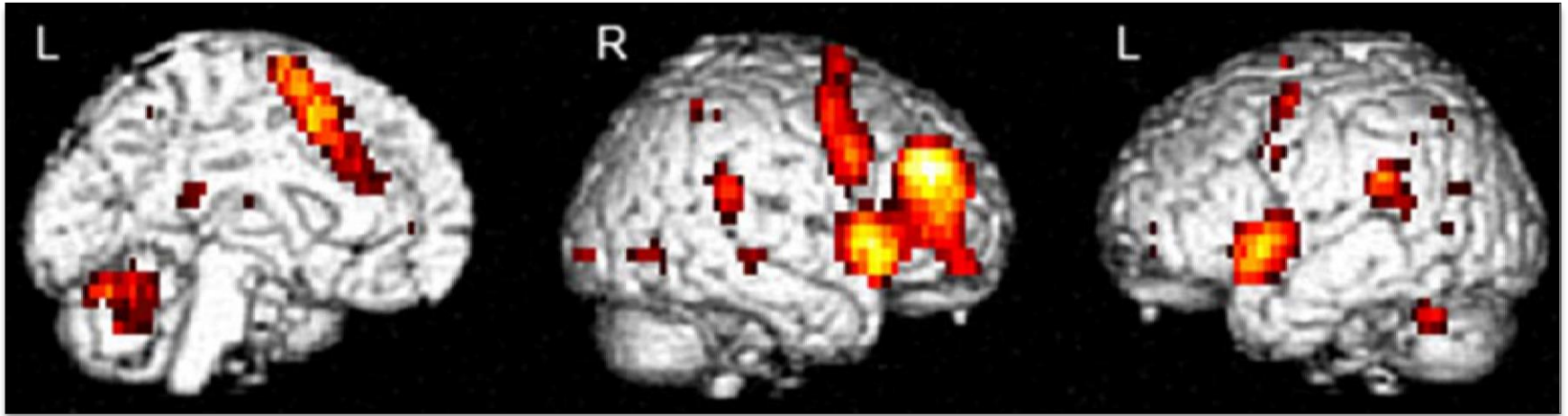
- No significant differences on Go/No-Go task
- Differences between activation for the “Press all letters except for X” (Response inhibition task) minus “Rest” activation in a dose-response relationship
  - More marijuana use → greater activation in areas of the premotor cortex, right thalamus, and right middle frontal gyrus

# Activation differences between Cannabis Users and Non-Users



## Working Memory Task

# Activation differences between Cannabis Users and Non-Users



## Response Inhibition Task

Cognitive Impairments: Adolescent MJ users need to use more cognitive capacity/more cognitive effort to perform as well on tasks as their non-MJ-using peers

# Cannabis as a risk factor for psychosis: systematic review

David M. Semple *Division of Psychiatry, University of Edinburgh, Edinburgh, UK.*

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Stephen M. Lawrie *Division of Psychiatry, University of Edinburgh, Edinburgh, UK.*

## Abstract

Various lines of evidence suggest an association between cannabis and psychosis. Five years ago, the only significant case-control study addressing this question was the Swedish Conscript Cohort. Within the last few years, other studies have emerged, allowing the evidence for cannabis as a risk factor to be more systematically reviewed and

psychosis. Seven were included in the meta-analysis, with a derived odds ratio (fixed effects) of 2.9 (95% confidence interval = 2.4–3.6). No evidence of publication bias or heterogeneity was found. Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with

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CA and New Delhi  
10.1177/0269881105049040

## Effects of marijuana use on psychosis »»

# Meta-analysis of 11 studies examining the relationship between cannabis use and psychosis

- ▶ Dose-related effect of cannabis use with vulnerable groups including individuals who used cannabis during adolescence, those who had previously experienced psychotic symptoms, and those at high genetic risk of developing schizophrenia.
- ▶ Available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms.
- ▶ Six case-control studies found psychotic symptoms in cannabis users vs. non-users in both 'high risk' and 'general' population samples
- ▶ Dunedin Birth Cohort Study (Arseneault *et al.*, 2002) found that, even when psychotic symptoms at age 11 years were controlled for, cannabis users by age 15 years and by age 18 years had significantly more 'schizophrenia symptoms' compared to controls (although data did not permit calculation of ORs).

# Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction

Avshalom Caspi, Terrie E. Moffitt, Mary Cannon, Joseph McClay, Robin Murray, HonaLee Harrington, Alan Taylor, Louise Arseneault, Ben Williams, Antony Braithwaite, Richie Poulton, and Ian W. Craig

**Background:** Recent evidence documents that cannabis use by young people is a modest statistical risk factor for psychotic symptoms in adulthood, such as hallucinations and delusions, as well as clinically significant schizophrenia. The vast majority of cannabis users do not develop psychosis, however, prompting us to hypothesize that some people are genetically vulnerable to the deleterious effects of cannabis.

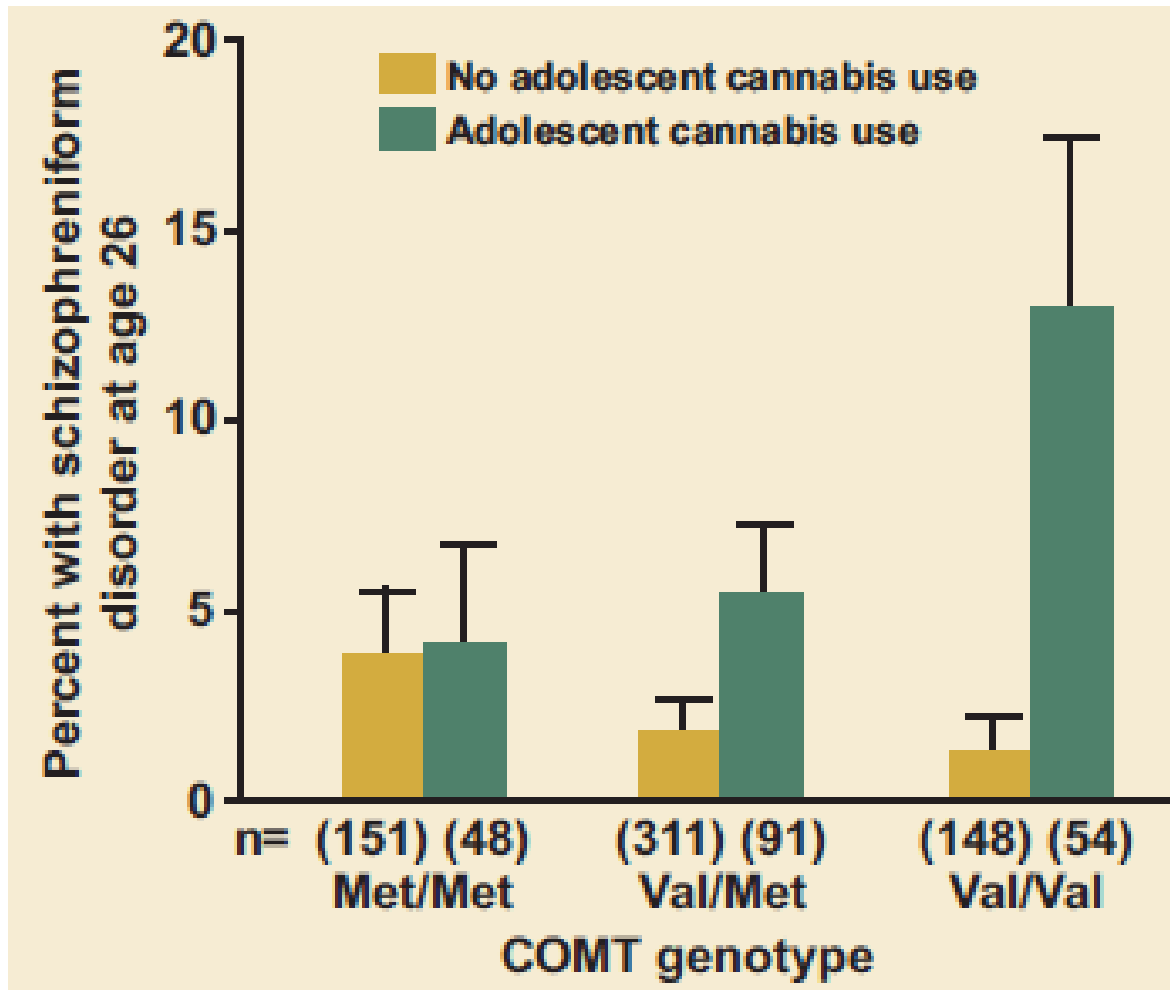
**Methods:** In a longitudinal study of a representative birth cohort followed to adulthood, we tested why cannabis use is associated with the emergence of psychosis in a minority of users, but not in others.

**Results:** A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis. Carriers of the COMT valine<sup>158</sup> allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis use had no such adverse influence on individuals with two copies of the methionine allele.

**Conclusions:** These findings provide evidence of a gene  $\times$  environment interaction and suggest that a role of some susceptibility genes is to influence vulnerability to environmental pathogens.

Influence of adolescent marijuana use on adult psychosis is affected by genetic variables >>

# Influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene



- Individuals with copies of the Val variant have a higher risk of developing schizophrenic-type disorders if they used cannabis during adolescence
- Those with only the Met variant were unaffected by cannabis use.

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# Confirmation that the *AKT1* (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users

Marta Di Forti, Conrad Iyegbe, Hannah Sallis, Anna Kolliakou, M. Aurora Falcone, Alessandra Paparelli, Miriam Sirianni, Caterina La Cascia, Simona A. Stilo, Tiago Reis Marques, Rowena Handley, Valeria Mondelli, Paola Dazzan, Carmine Pariante, Anthony S. David, Craig Morgan, John Powell, and Robin M. Murray

**Background:** Cannabis use is associated with an increased risk of psychosis. One study has suggested that genetic variation in the *AKT1* gene might influence this effect.

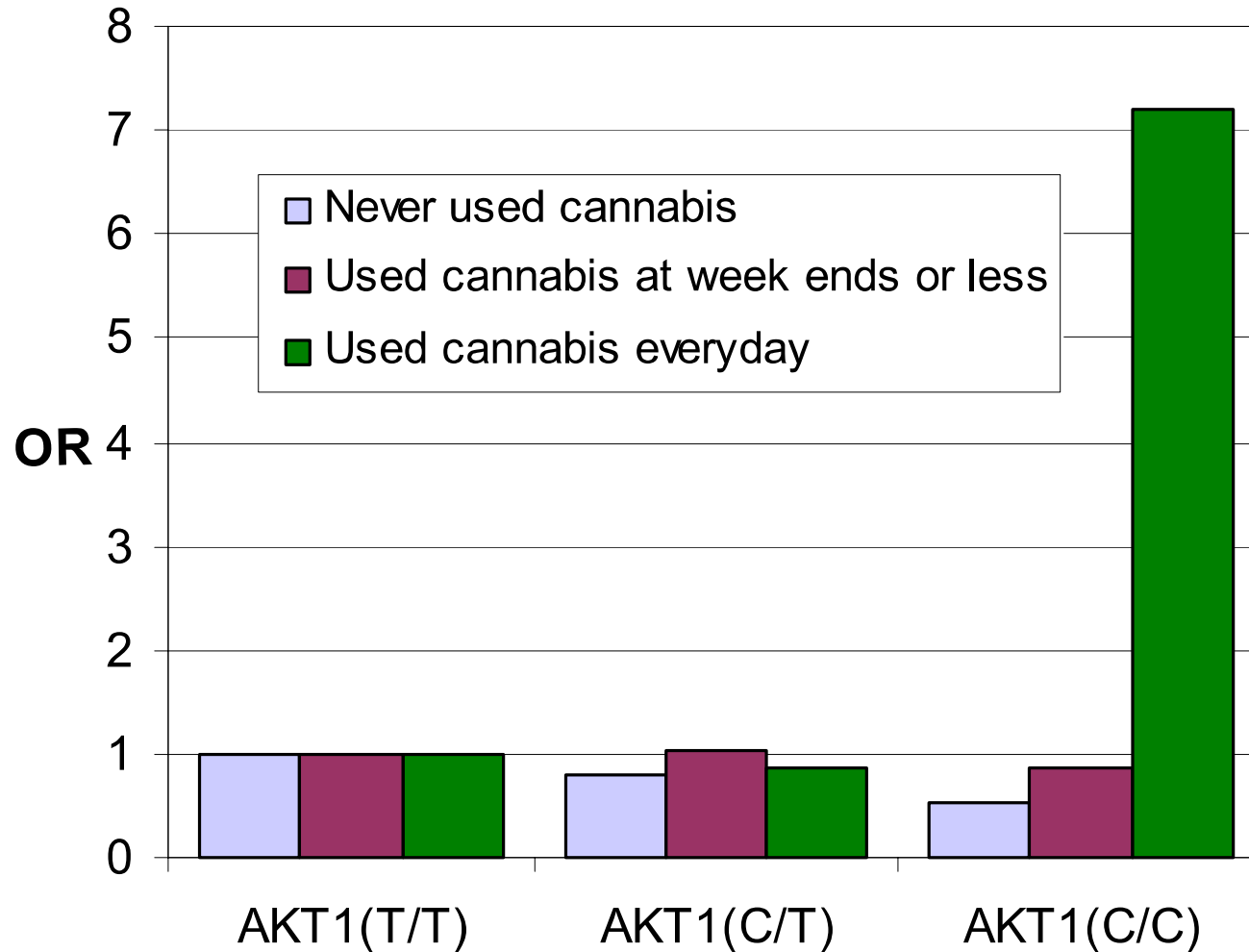
**Methods:** In a case-control study of 489 first-episode psychosis patients and 278 control subjects, we investigated the interaction between variation at the *AKT1* rs2494732 single nucleotide polymorphism and cannabis use in increasing the risk of psychosis.

**Results:** The rs2494732 locus was not associated with an increased risk of a psychotic disorder, with lifetime cannabis use, or with frequency of use. We did, however, find that the effect of lifetime cannabis use on risk of psychosis was significantly influenced by the rs2494732 locus (likelihood ratio statistic for the interaction = 8.54;  $p = .014$ ). Carriers of the C/C genotype with a history of cannabis use showed a greater than twofold increased likelihood of a psychotic disorder (odds ratio = 2.18 [95% confidence interval: 1.12, 4.31]) when compared with users who were T/T carriers. Moreover, the interaction between the rs2494732 genotype and frequency of use was also significant at the 5% level (likelihood ratio = 13.39;  $p = .010$ ). Among daily users, C/C carriers demonstrated a sevenfold increase in the odds of psychosis compared with T/T carriers (odds ratio = 7.23 [95% confidence interval: 1.37, 38.12]).

**Conclusions:** Our findings provide strong support for the initial report that genetic variation at rs2494732 of *AKT1* influences the risk of developing a psychotic disorder in cannabis users.

Whether adolescent marijuana use can contribute to developing psychosis later in adulthood may depend on existing genetically based vulnerability >>

# AKT1 Gene Variants and Psychosis



- Daily users with C/C variant have seven times higher risk of developing psychosis than infrequent marijuana users or nonusers
- Risk for users with T/T variant unaffected by marijuana use



intoxication

## Cannabis Effects on Driving Skills

Rebecca L. Hartman<sup>1,2</sup> and Marilyn A. Huestis<sup>1\*</sup>

**BACKGROUND:** Cannabis is the most prevalent illicit drug identified in impaired drivers. The effects of cannabis continue to be debated, making proscription difficult. Historically, delays in prosecution, evaluating the inactive  $\Delta^9$ -tetrahydrocannabinol (THC) metabolite 11-nor-9- $\alpha$ -carboxy-THF, and polydrug use have complicated evaluations of driver impairment after

ingestion of cannabis. Cannabis use is associated with substantial driving impairment, particularly in occasional smokers. Future cannabis-and-driving research should emphasize challenging tasks, such as divided attention, and include occasional and chronic daily cannabis smokers.

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Risk of motor vehicle accident increase about 2x after smoking MJ. Critical tracking tasks, reaction times. Divided-attention tasks, lane-position variability all show MJ-induced impairments. **Dose dependent. Even among more tolerant regular users, impairments persist.**

view and evaluate the current literature on driving, highlighting the epidemiologic and experimental data. Epidemiologic data show a risk of involvement in a motor vehicle accident increases approximately 2-fold after smoking. The adjusted risk of driver culpability is substantially increased with increasing THC concentrations. Studies that have examined the biological matrix have not shown an association between cannabis and crash risk. Experiments show that drivers attempt to compensate for impairment slowly after smoking cannabis, but performance decreases with increasing task complexity. Driving increases lane weaving and impairment in critical-tracking tests, reaction-time tasks, and lane-position variability. Despite purported tolerance in frequent smokers, complex tasks still show impairment. Combining cannabis with alcohol enhances impairment, especially lane weaving.

**SUMMARY:** Differences in study designs frequently account for inconsistencies in results between studies. Participant-selection bias and confounding factors attenuate ostensible cannabis effects, but the association with MVA often retains significance. Evidence suggests recent smoking and/or blood THC concentrations 2–5

Nearly two thirds of US trauma center admissions are due to motor vehicle accidents (MVAs),<sup>3</sup> with almost 60% of such patients testing positive for drugs or alcohol (1). In 2010, 11.4% of Americans 12 years or older drove under the influence of alcohol, and 10.6 million drove under the influence of illicit drugs (2). Despite real or perceived impairment, individuals report a willingness to drive if there is a good reason (3, 4) or if they believe they are tolerant (5). Alcohol and cannabis are the drugs most frequently detected (6).

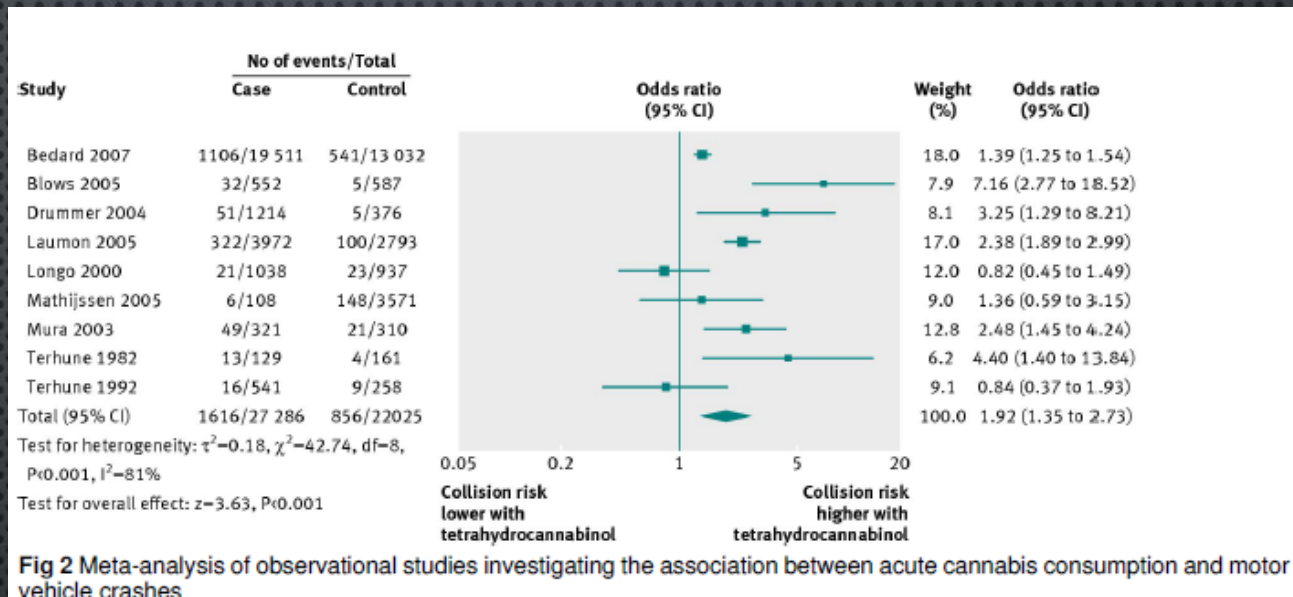
Cannabis is the most widely consumed illicit substance worldwide (2). In 2009, 125–203 million individuals 15–64 years of age ingested cannabis in the previous year (7). In the US in 2010, 6.9% of individuals  $\geq 12$  years old had smoked cannabis in the previous month (2). The 2007 National Roadside Survey reported cannabis as the most common illicit drug quantified in drivers' blood or oral fluid (OF), with 8.6% of nighttime drivers testing positive for  $\Delta^9$ -tetrahydrocannabinol (THC) (6, 8). Thus, driving under the influence of cannabis (DUIC) is a growing public health concern.

The acute psychological effects of cannabinoids include euphoria, dysphoria, sedation, and altered perception (9). The intensity of euphoria/dysphoria varies with dose, administration route, and vehicle; expectations of effects; and the cannabis smoker's environment and personality. Cannabis is associated with subjective physical discomfort and effort, as well as with lethargy (10). Acute cannabis intoxication produces dose-related impairment in cognitive and psychomotor functioning, and it can produce risk-taking behavior that can impair driving skills (11, 12). Dose refers to

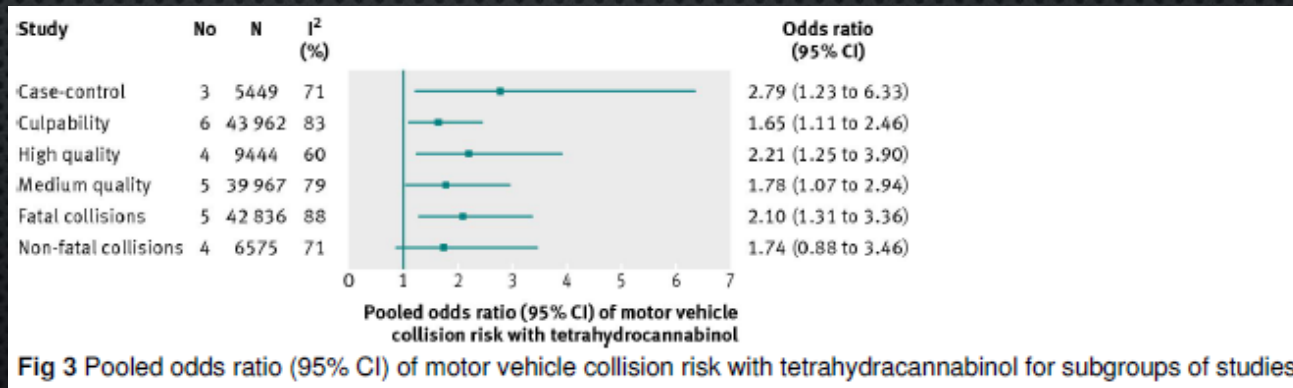
<sup>1</sup>Chemistry and Drug Metabolism, Intramural Research Program, National Institute on Drug Abuse, Bethesda, MD

# PUBLIC HEALTH RISKS OF MARIJUANA

## MOTOR VEHICLE COLLISION RISK OVER ALL STUDIES



## MOTOR VEHICLE COLLISION RISK BY TYPE OF STUDY



Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ: British Medical Journal*, 344.

RESEARCH ARTICLE

# Correlates of Marijuana Drugged Driving and Openness to Driving While High: Evidence from Colorado and Washington

Kevin C. Davis\*, Jane Allen, Jennifer Duke, James Nonnemaker, Brian Bradfield, Matthew C. Farrelly, Paul Shafer, Scott Novak

RTI International, Research Triangle Park, NC, United States of America

\* [kcdavis@rti.org](mailto:kcdavis@rti.org)

## Results

Prevalence of past-year driving while under the influence of marijuana was 43.6% among

**Method:** Online survey of of past month MJ users in WA and CO states (N=865)

**Results:** Prevalence of past-yr driving under influence of MJ was 44%  
Prevalence of driving within 1 hour of using MJ 5+ times in past month = 24%

69% lower odds of driving if perceived risky  
37% lower odds of driving if had knowledge of MJ DUI laws

# Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado\*

Stacy Salomonsen-Sautel<sup>1</sup>, Sung-Joon Min<sup>1</sup>, Joseph T. Sakai<sup>1</sup>, Christian Thurstone<sup>1,2</sup>, and Christian Hopfer<sup>1</sup>

<sup>1</sup>Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045

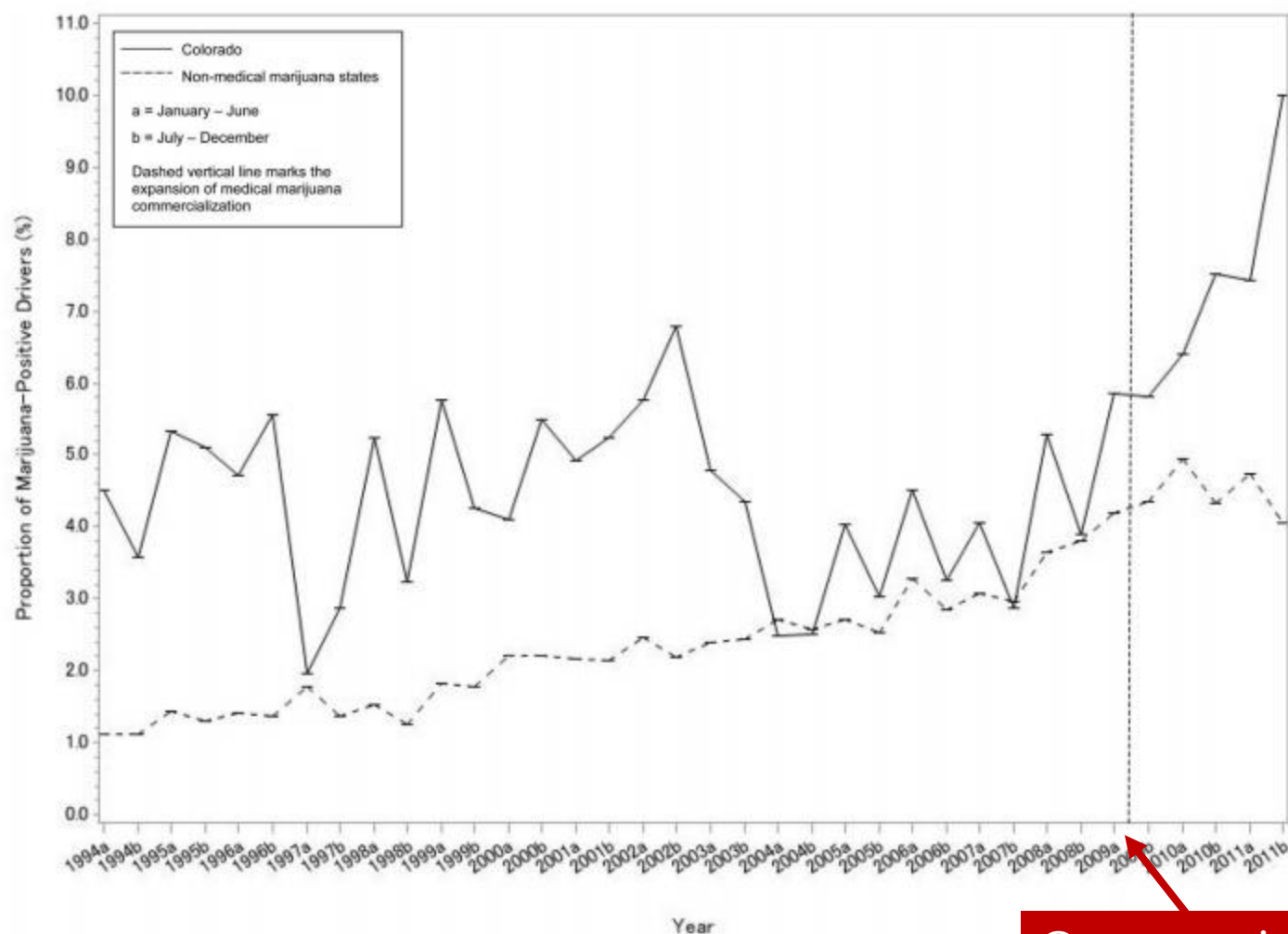
<sup>2</sup>Denver Health and Hospital Authority, Denver, CO, 80204

## Abstract

**Background**—Legal medical marijuana has been commercially available on a widespread basis in Colorado since mid-2009; however, there is a dearth of information about the impact of marijuana commercialization on impaired driving. This study examined if the proportions of drivers in a fatal motor vehicle crash who were marijuana-positive and alcohol-impaired, respectively, have changed in Colorado before and after mid-2009 and then compared changes in Colorado with 34 non-medical marijuana states (NMMS).

**Methods**—Thirty-six 6-month intervals (1994–2011) from the Fatality Analysis Reporting System were used to examine temporal changes in the proportions of drivers in a fatal motor vehicle crash who were alcohol-impaired ( $\geq 0.08$  g/dl) and marijuana-positive, respectively. The pre-commercial marijuana time period in Colorado was defined as 1994–June 2009 while July 2009–2011 represented the post-commercialization period.

**Results**—In Colorado, since mid-2009 when medical marijuana became commercially available and prevalent, the trend became positive in the proportion of drivers in a fatal motor vehicle crash who were marijuana-positive (change in trend, 2.16 (0.45),  $p < 0.0001$ ); in contrast, no significant changes were seen in NMMS. For both Colorado and NMMS, no significant changes were seen in the proportion of drivers in a fatal motor vehicle crash who were alcohol-impaired.



Commercialization of medical MJ in CO

**Figure 2.**

Proportion of drivers in a fatal motor vehicle crash who were marijuana-positive in Colorado and 34 states without medical marijuana laws from 1994–2011

# Summary of Research on Adverse effects of cannabis use

Table 1 Summary of major adverse health outcomes of recreational cannabis use.

|                        | <i>Evidence</i> | <i>Level of evidence</i> | <i>Strength of effect</i> |
|------------------------|-----------------|--------------------------|---------------------------|
| <i>Acute effects</i>   |                 |                          |                           |
| Fatal overdose         | +++             | No case reports          | 0                         |
| Road traffic crashes   | ++              | Cohort and case control  | 2-fold                    |
| Low birth weight       | ++              | Cohort                   |                           |
| <i>Chronic effects</i> |                 |                          |                           |
| Dependence             | +++             | Cohort studies           | 1 in 10 among ever users  |
| Educational outcomes   | ++              | Cohort and case control  | 2-fold in regular users   |
| Cognitive impairment   | ++              | Cohort and case control  | Difficult to quantify     |
| Psychosis              | ++              | Cohort studies           | 2-fold in regular users   |
| Depression             | +?              | Cohort studies           | Probable confounding      |
| Suicide                | +?              | Cohort studies           | 2-fold in regular users   |
| Chronic bronchitis     | ++              | Cohort studies           | 2-fold in regular users   |
| Respiratory impairment | +?              | Cohort studies           | Mixed                     |
| Cardiovascular disease | ++              | Cohort and case control  | 3–4-fold for MI           |
| <i>Cancers</i>         |                 |                          |                           |
| Testicular cancers     | ++              | Case-control             | 2–3-fold                  |
| Respiratory cancers    | +?              | Case-control             | Confounded by smoking     |

## Acute/Intoxication Use

- Unlikely to produce fatal overdoses as do opioids or alcohol
- Doubled risk of car crashes if cannabis users drive while intoxicated
- Increases substantially if users also consume intoxicating doses of alcohol
- Maternal cannabis use in pregnancy associated with modest birth weight reduction

## Chronic Use

- Addiction syndrome
  - 1 in 10 of all users
  - 1 in 6 users who start in adolescence
- Doubles risk of experiencing psychotic symptoms and disorders
  - Personal or family history of psychotic disorders
  - Begin use in mid-teens
- Lower educational attainment than non-using peers
- More likely to use other illicit drugs

## Regular use beginning in adolescence and continuing throughout young adulthood

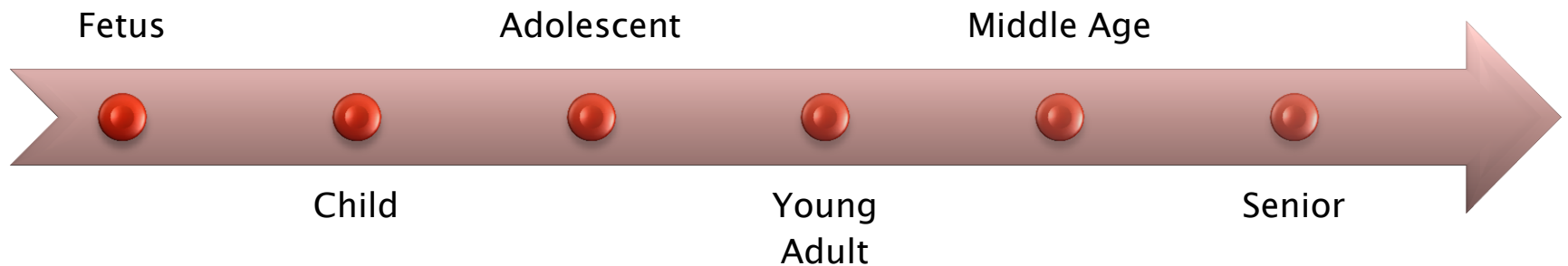
- Likely to produce cognitive impairment
- Mechanism and reversibility of the impairment is unclear
- Doubles risk of being diagnosed with schizophrenia or reporting psychotic symptoms in adulthood (relationships persist after controlling for plausible confounders in well-designed studies, but some researchers question whether adverse effects are related causally to cannabis or explained by shared risk factors)

## Physical Health Outcomes

- High risk of developing chronic bronchitis
- Probably increase in risk of myocardial infarction in middle-aged adults

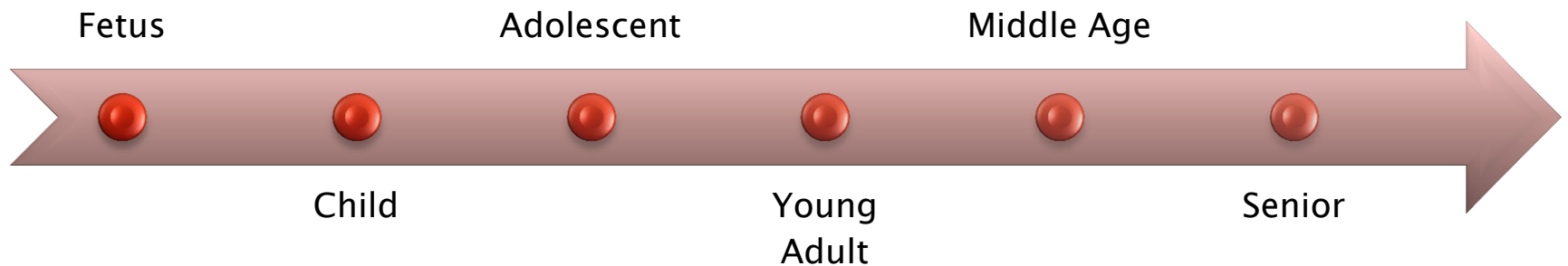
# Approach and Context

## A Life Course Perspective



The life course perspective has the advantage of recognizing developmental stages as factors facilitating or inhibiting change and continuity, and/or protective and risk factors, that may differ across the life span (Hser & Anglin, 2008).

# Why is A Life Course Perspective so important in public health and disease management??

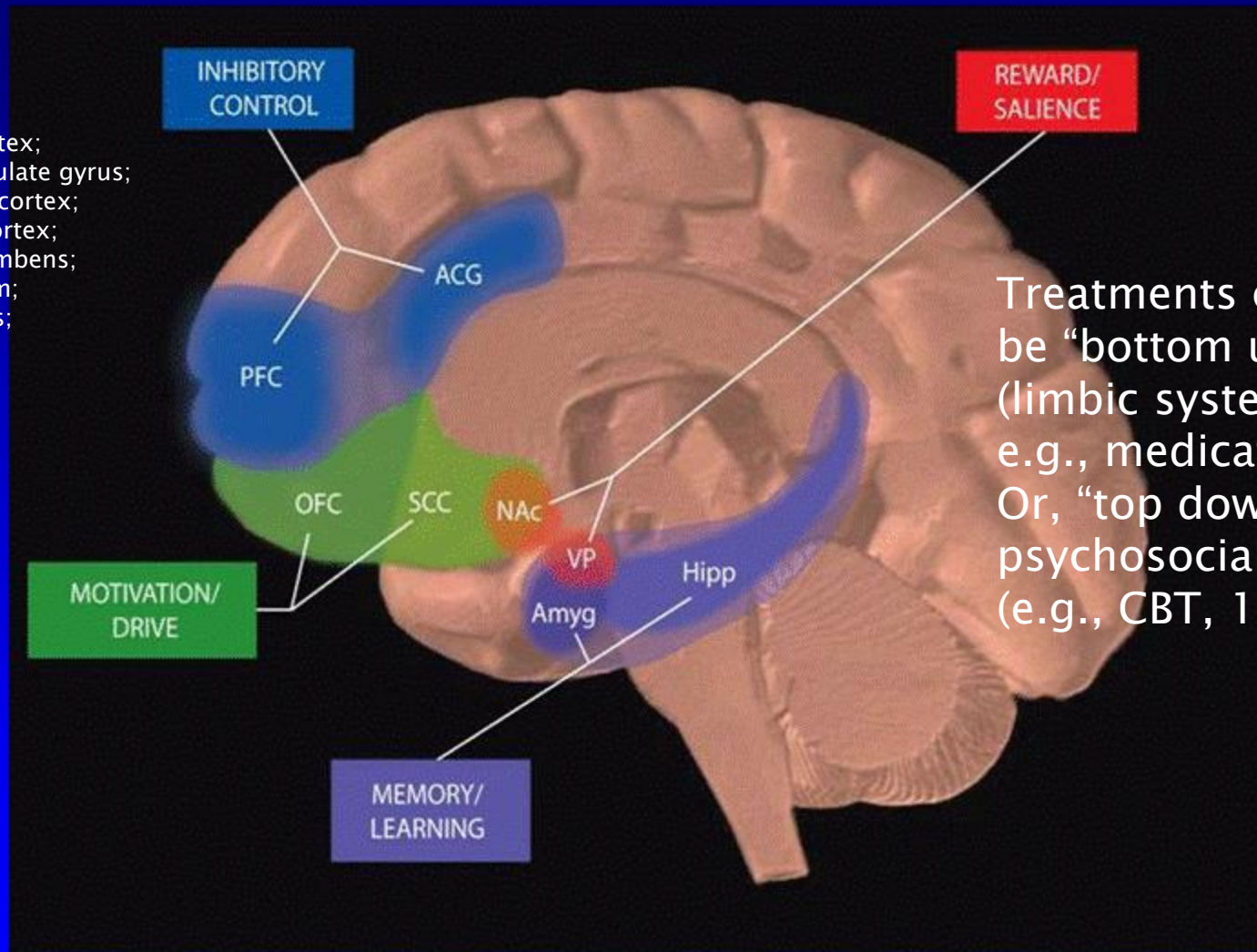


The life course perspective has the advantage of recognizing developmental stages as factors facilitating or inhibiting change and continuity, and/or protective and risk factors, that may differ across the life span (Hser & Anglin, 2008).

# *Circuits Involved In Drug Abuse and Addiction*

**Key:**

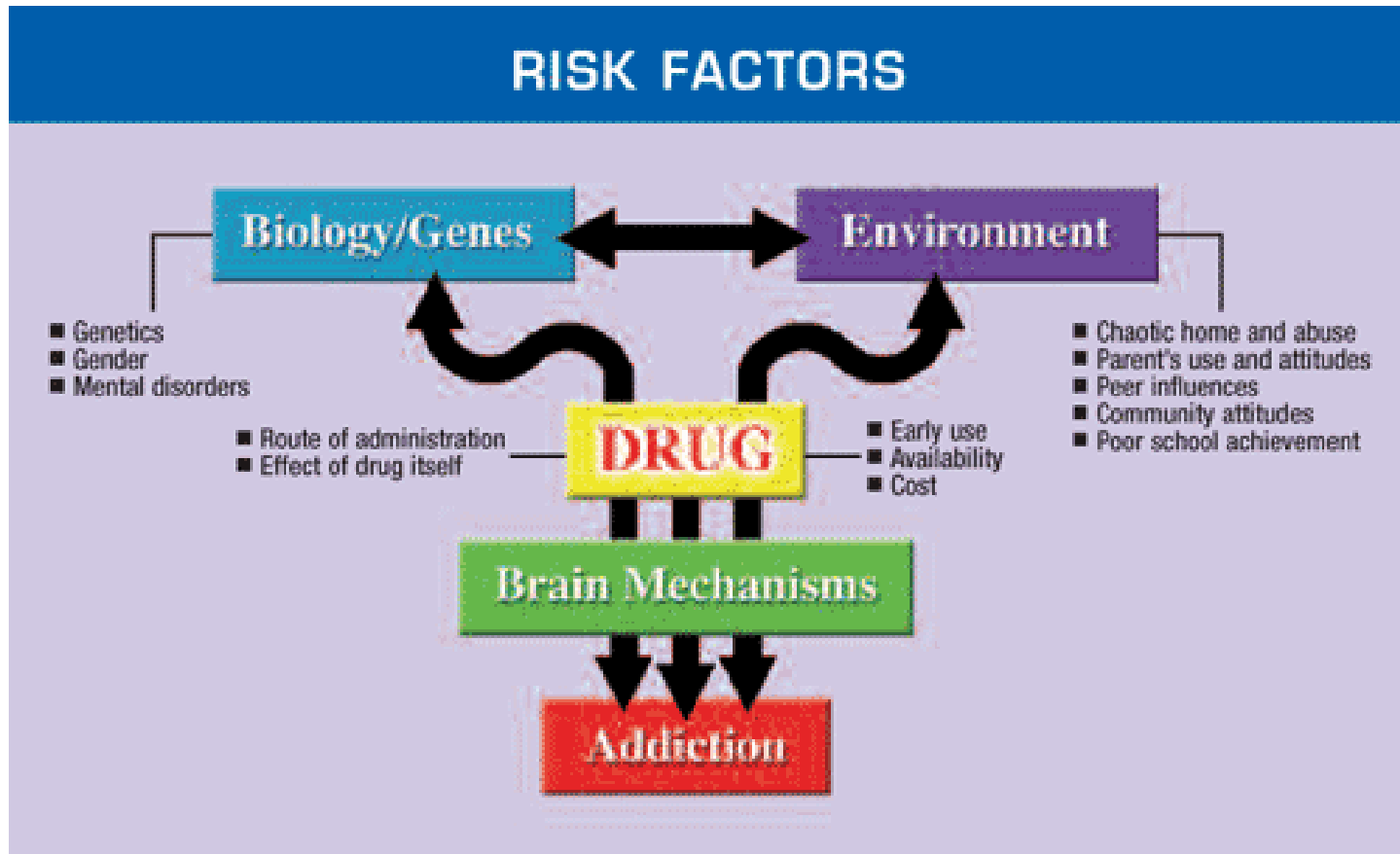
PFC – prefrontal cortex;  
ACG – anterior cingulate gyrus;  
OFC – orbitofrontal cortex;  
SCC – subcallosal cortex;  
NAc – nucleus accumbens;  
VP – ventral pallidum;  
Hipp – hippocampus;  
Amyg – amygdala.



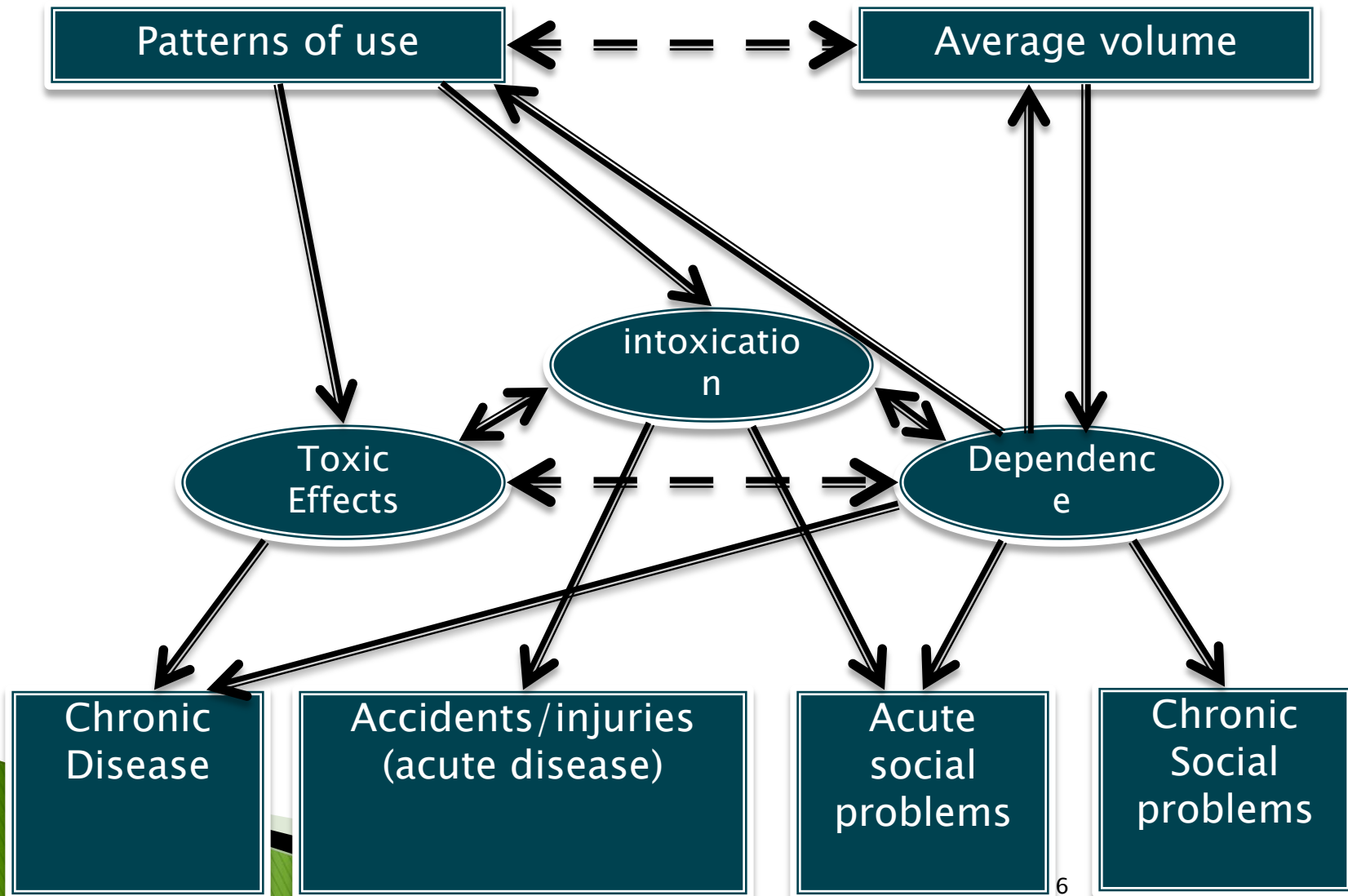
Treatments can be “bottom up” (limbic system; e.g., medications) Or, “top down” psychosocial treatments (e.g., CBT, 12-step)

**All of these brain regions must be considered in developing strategies to effectively treat addiction**

# RISK FACTORS IN ADDICTION



# Mediators of substance-related harm: Toxicity, Intoxication, and Dependence (Babor et al, 2010)

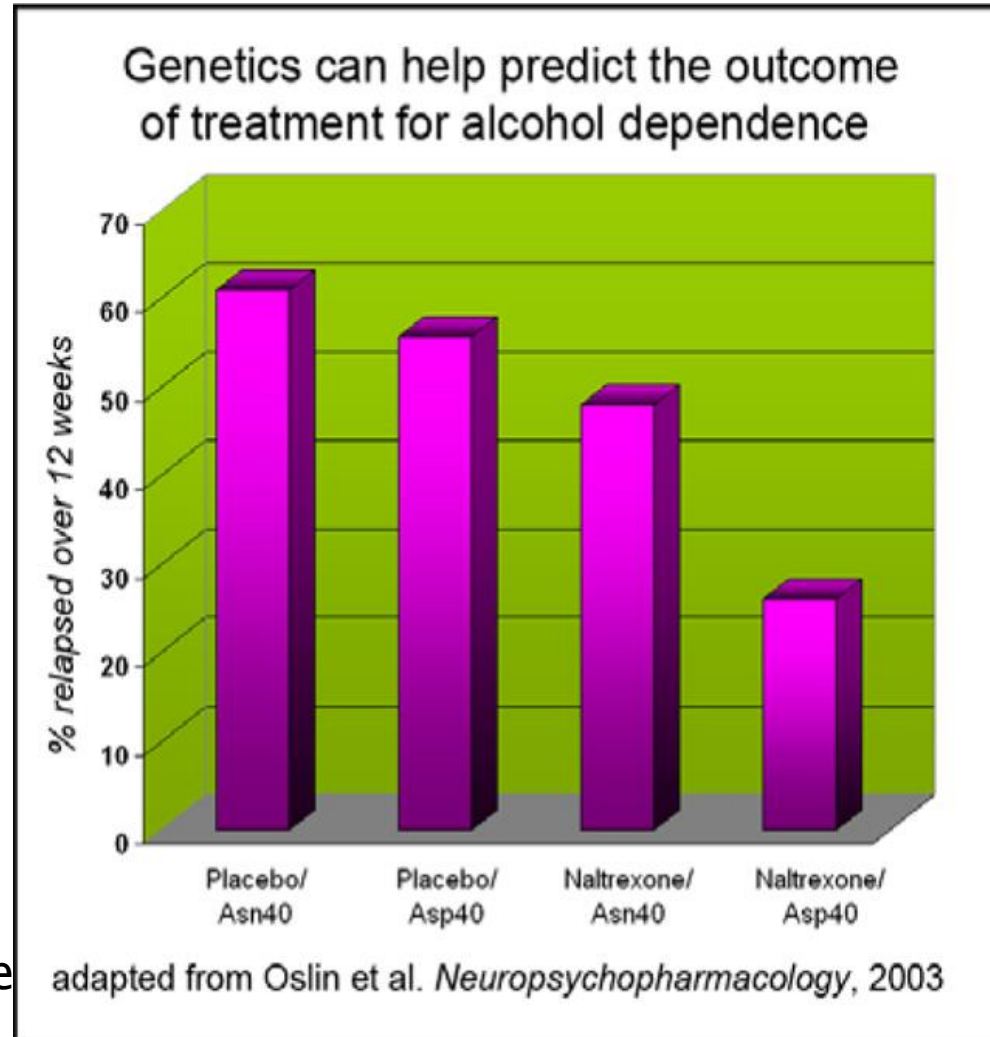


# If drugs are so pleasurable, Why aren't we all addicted?

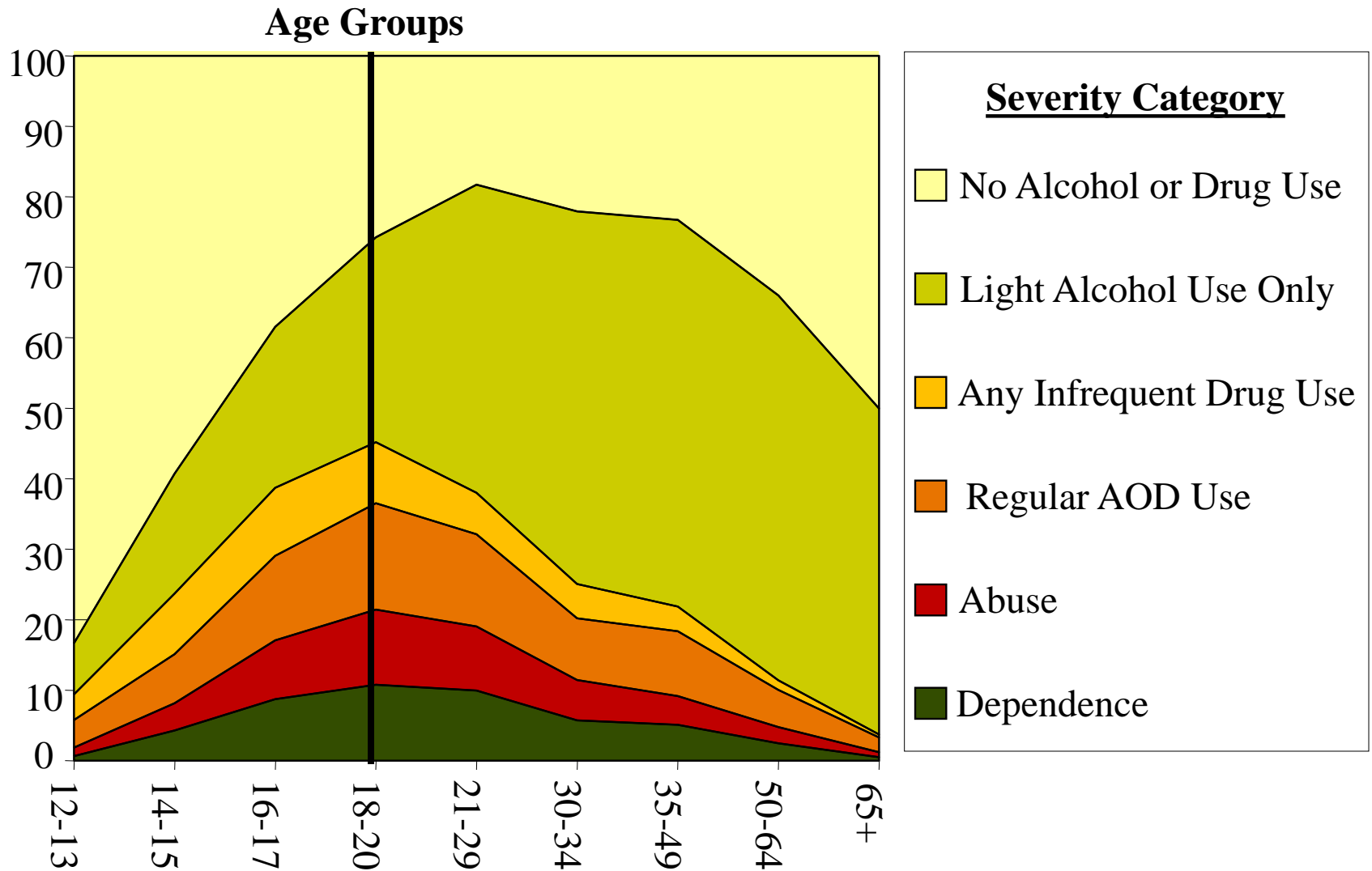
Genetically mediated Reward sensitivity...



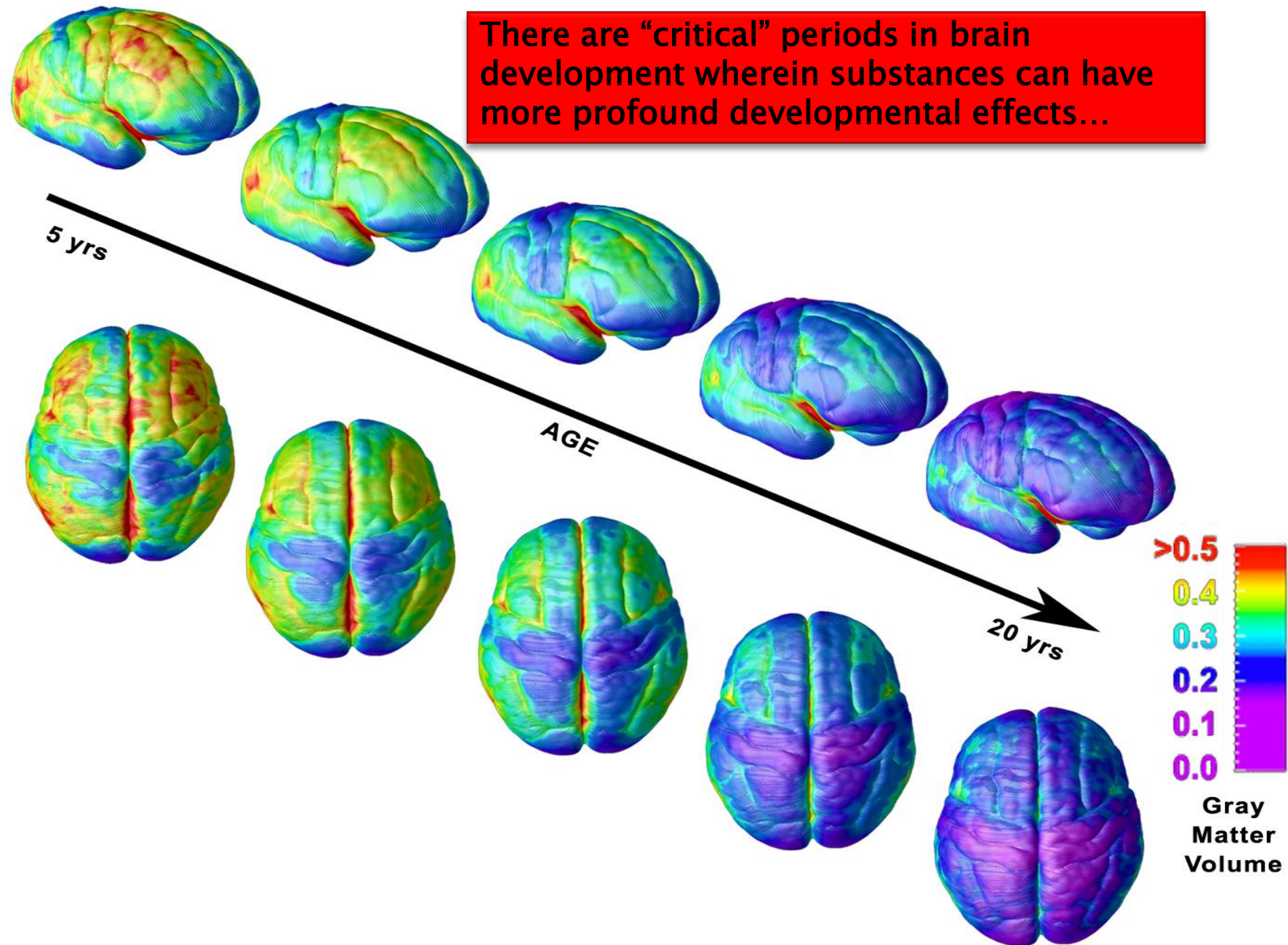
- Approx. 50% of the risk for addiction is genetic
- Genetic differences affect the degree of reward people experience from different substances/activities
- Genes also can be used to enhance the effectiveness in matching treatments



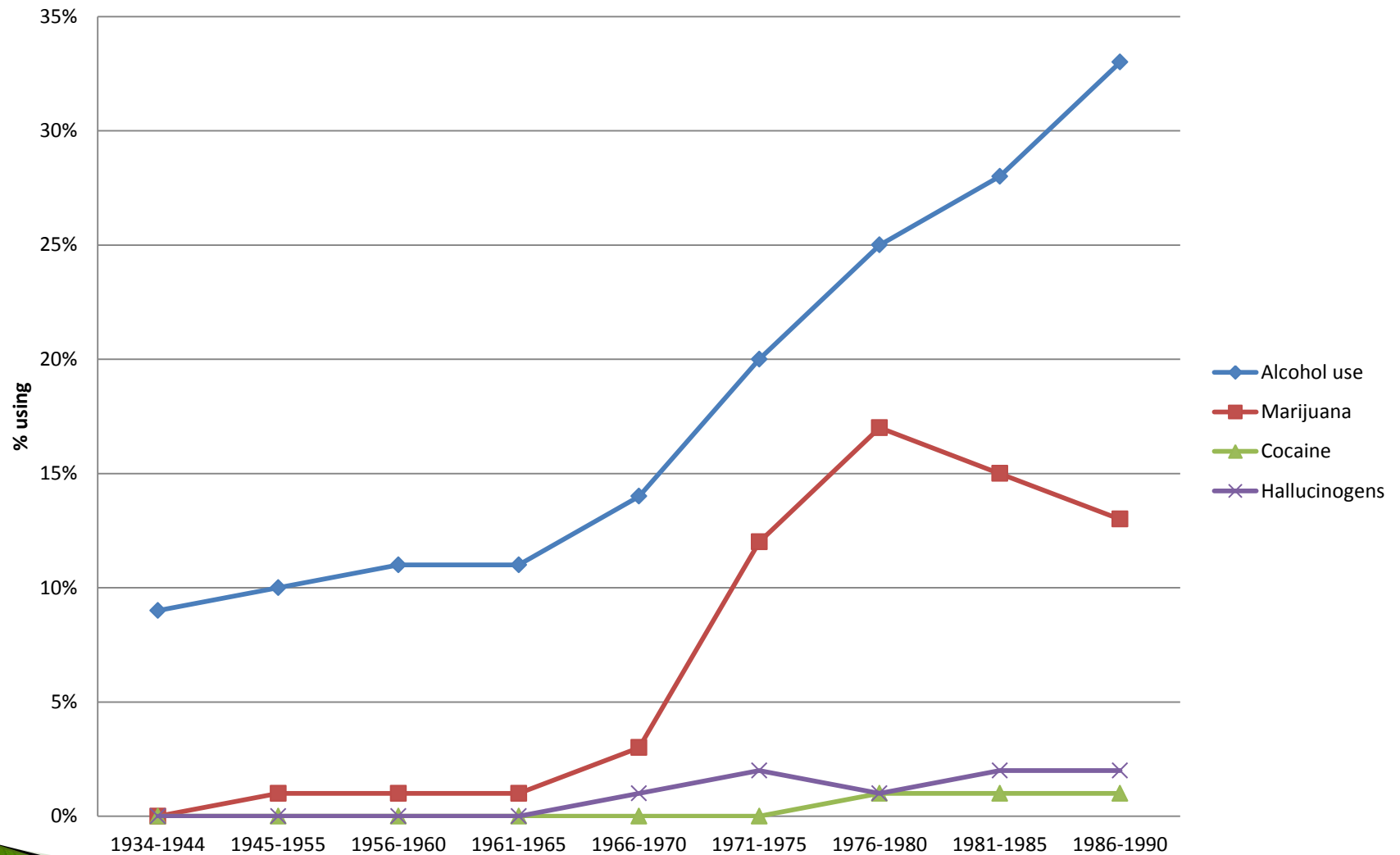
# Substance Use and Problem Onset and Offset



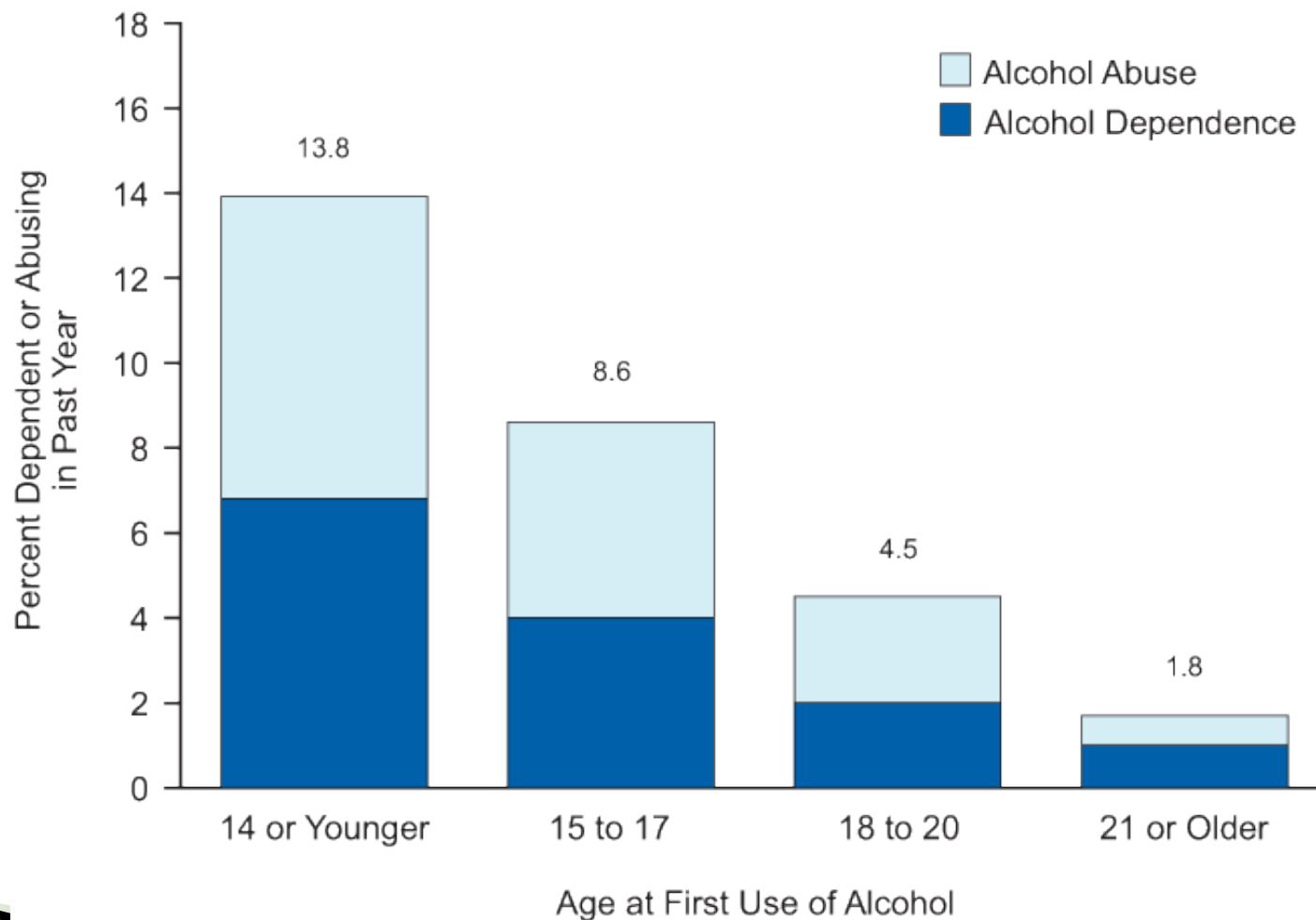
There are “critical” periods in brain development wherein substances can have more profound developmental effects...



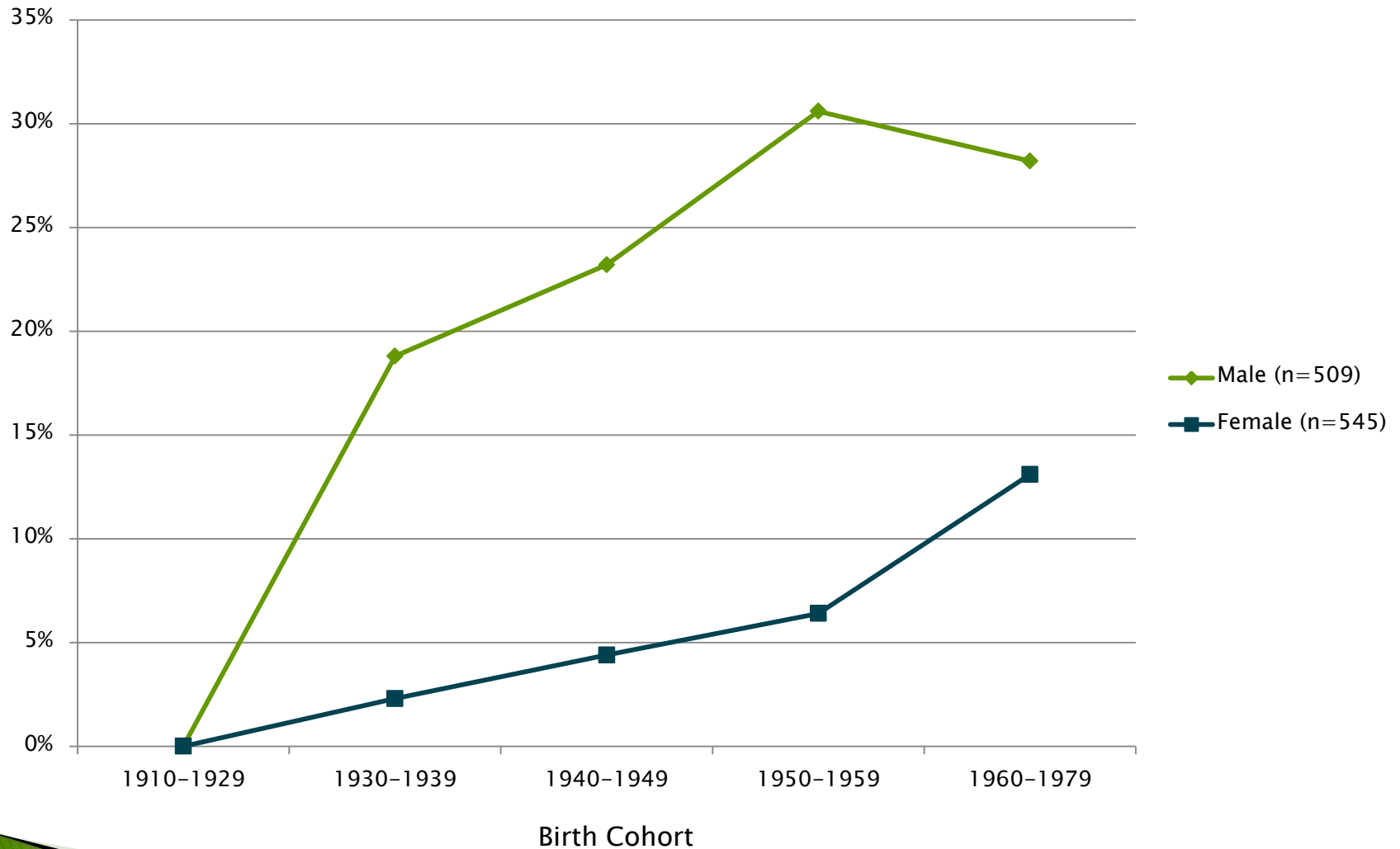
# % Using prior to age 15



# Past Year Alcohol Dependence or Abuse among Adults (21 or older), by Age at First Use of Alcohol: 2011



# % meeting DSM-III-R lifetime alcohol dependence criteria



Adapted from: Rice, J. P., Neuman, R. J., Saccone, N. L., Corbett, J., Rochberg, N., Hesselbrock, V., & ... Reich, T. (2003). *Alcoholism: Clinical And Experimental Research*, 27(1), 93-99.

# Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier<sup>a,b,1</sup>, Avshalom Caspi<sup>a,b,c,d,e</sup>, Antony Ambler<sup>e,f</sup>, HonaLee Harrington<sup>b,c,d</sup>, Renate Houts<sup>b,c,d</sup>, Richard S. E. Keefe<sup>d</sup>, Kay McDonald<sup>f</sup>, Aimee Ward<sup>f</sup>, Richie Poulton<sup>f</sup>, and Terrie E. Moffitt<sup>a,b,c,d,e</sup>

<sup>a</sup>Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, <sup>b</sup>Department of Psychology and Neuroscience, and <sup>c</sup>Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; <sup>d</sup>Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; <sup>e</sup>Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and <sup>f</sup>Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

**Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants**

**neuropsychological test performance after a period of abstinence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is re-**

Even when recent MJ use was taken into account along with other confounds heavy use during teen years was associated with an 8 point drop in IQ

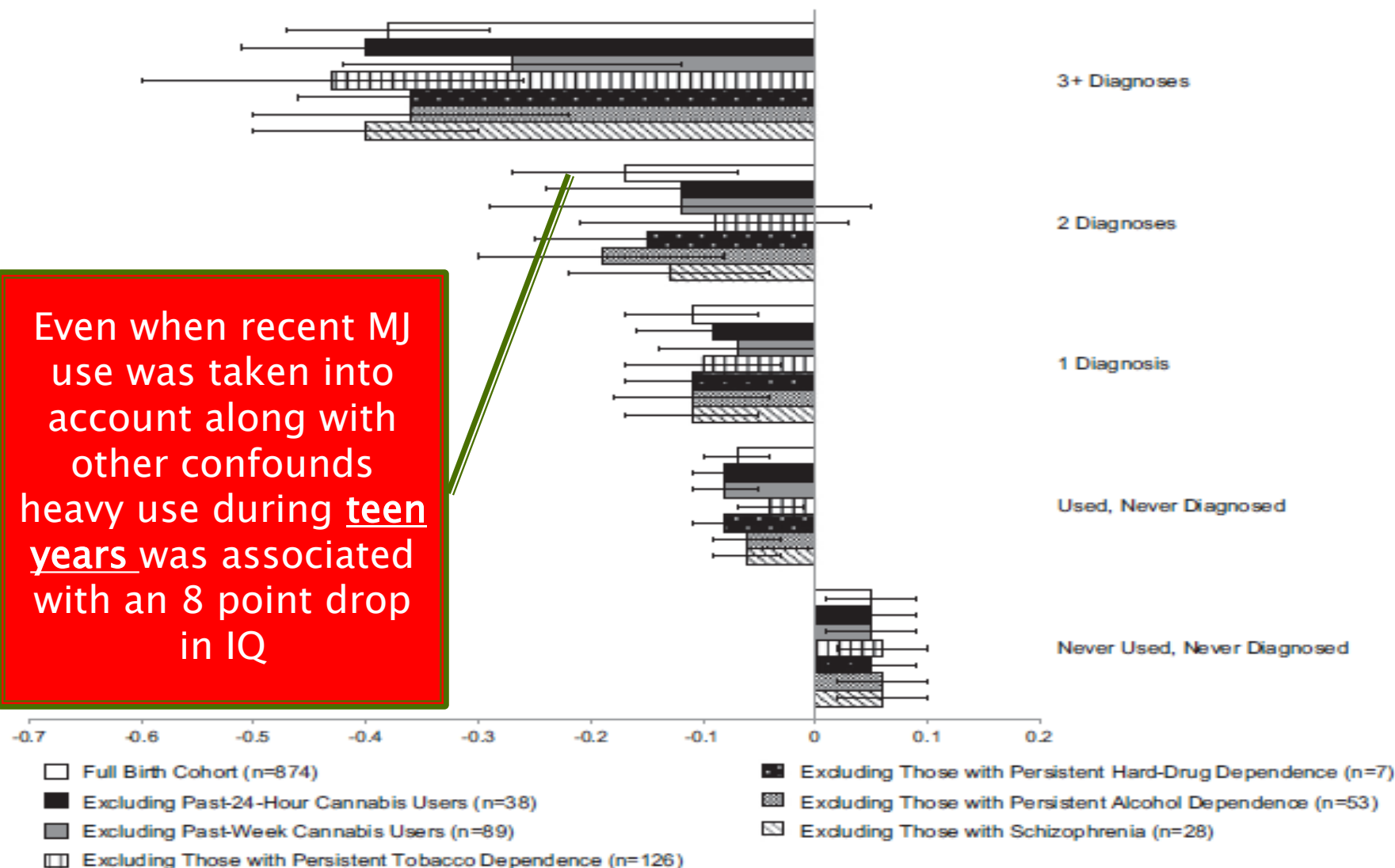
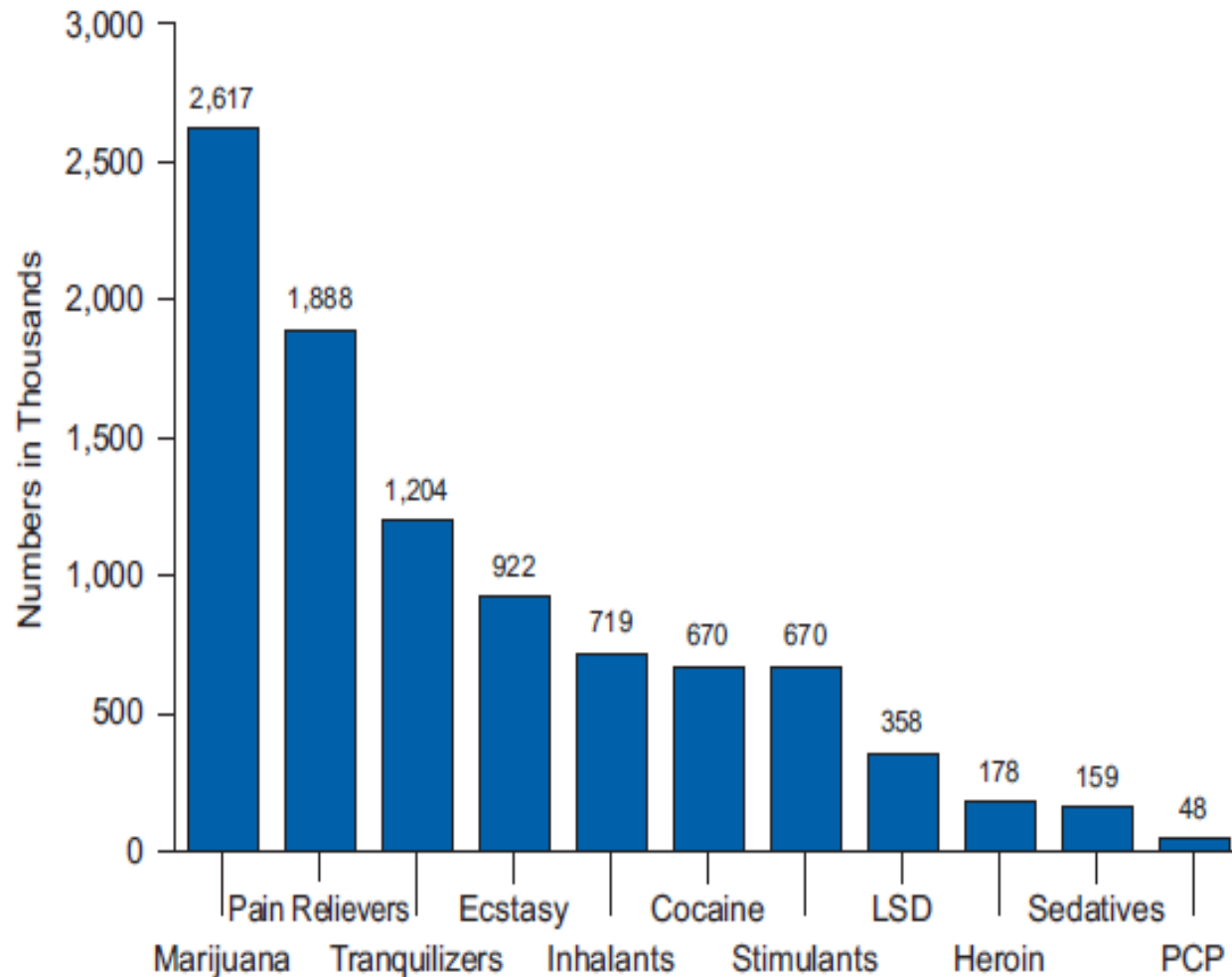


Fig. 1. Ruling out alternative explanations. Shown is change in full-scale IQ (in SD units) from childhood to adulthood as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. Change scores are presented for the full birth cohort and the cohort excluding (i) past 24-h cannabis users, (ii) past-week cannabis users, (iii) those with persistent tobacco dependence, (iv) those with persistent hard-drug dependence, (v) those with persistent alcohol dependence, and (vi) those with lifetime schizophrenia. Persistent tobacco, hard-drug, and alcohol dependence were each defined as dependence at three or more study waves. IQ decline could not be explained by other factors. Error bars = SEs.

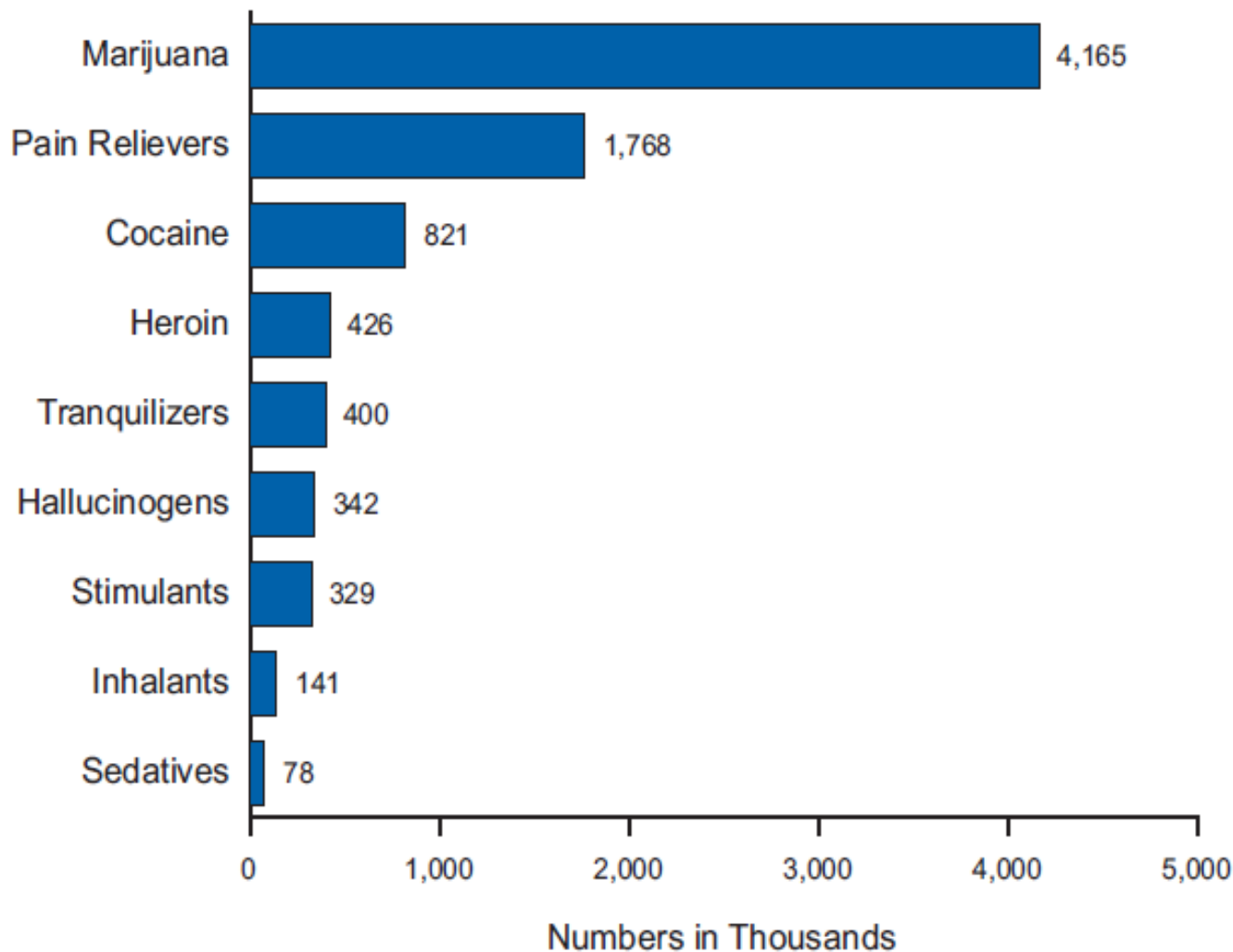
sizes, representing within-person IQ change as a function of tobacco, hard-drug, or alcohol dependence), and schizophrenia

## Past year initiates of specific drugs US Population

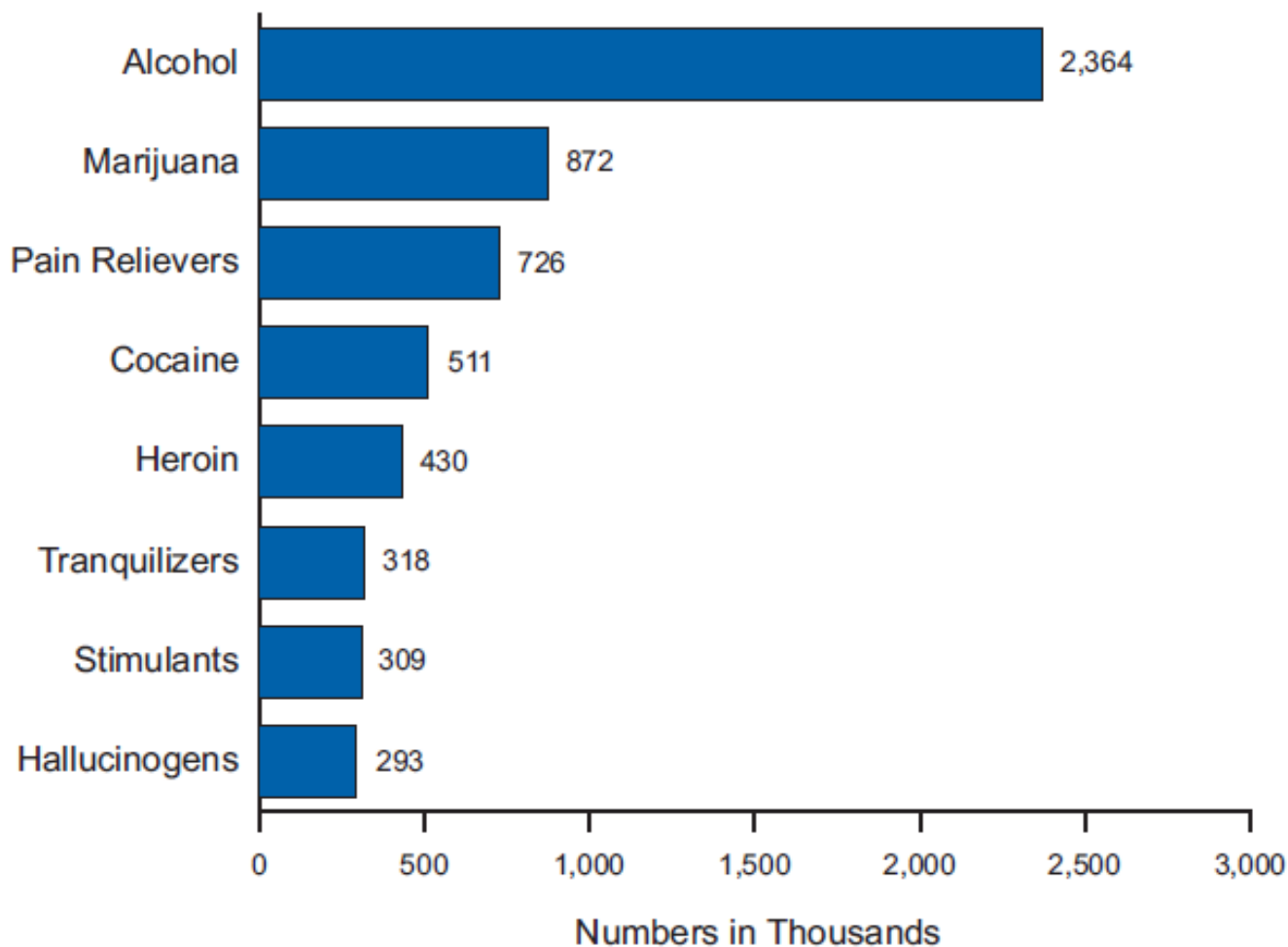


Note: Numbers refer to persons who used a specific drug for the first time in the past year, regardless of whether initiation of other drug use occurred prior to the past year.

**Figure 7.2 Specific Illicit Drug Dependence or Abuse  
in the Past Year among Persons Aged 12 or  
Older: 2011**



**Figure 7.8 Substances for Which Most Recent Treatment Was Received in the Past Year among Persons Aged 12 or Older: 2011**





# Young adult sequelae of adolescent cannabis use: an integrative analysis

Edmund Silins, L John Horwood, George C Patton, David M Fergusson, Craig A Olsson, Delyse M Hutchinson, Elizabeth Spry, John W Toumbourou, Louisa Degenhardt, Wendy Swift, Carolyn Coffey, Robert J Tait, Primrose Letcher, Jan Copeland, Richard P Mattick, for the Cannabis Cohorts Research Consortium\*

## Summary

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1: 286–93

See [Comment](#) page 249

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**Background** Debate continues about the consequences of adolescent cannabis use. Existing data are limited in statistical power to examine rarer outcomes and less common, heavier patterns of cannabis use than those already investigated; furthermore, evidence has a piecemeal approach to reporting of young adult sequelae. We aimed to provide a broad picture of the psychosocial sequelae of adolescent cannabis use.

**Methods** We integrated participant-level data from three large, long-running longitudinal studies from Australia and New Zealand: the Australian Temperament Project, the Christchurch Health and Development Study, and the Victorian Adolescent Health Cohort Study. We investigated the association between the maximum frequency of cannabis use before age 17 years (never, less than monthly, monthly or more, weekly or more, or daily) and seven developmental outcomes assessed up to age 30 years (high-school completion, attainment of university degree, cannabis dependence, use of other illicit drugs, suicide attempt, depression, and welfare dependence). The number of participants varied by outcome (N=2537 to N=3765).

**Findings** We recorded clear and consistent associations and dose-response relations between the frequency of adolescent cannabis use and all adverse young adult outcomes. After covariate adjustment, compared with individuals who had never used cannabis, those who were daily users before age 17 years had clear reductions in the odds of high-school completion (adjusted odds ratio 0.37, 95% CI 0.20–0.66) and degree attainment (0.38, 0.22–0.66), and

# Effects of adolescent marijuana use on adverse psychosocial outcomes during young adulthood »»

# Effects of adolescent marijuana use on adverse psychosocial outcomes during young adulthood

- ▶ Meta-analysis of three large, longitudinal studies in Australia and New Zealand:
  - Australian Temperament Project (ATP)
  - Christchurch Health and Development Study (CHDS)
  - Victorian Adolescent Health Cohort Study (VAHCS)
- ▶ Participants ages 13–30, from 2537–3765 depending on the analysis
- ▶ Baselines conducted between 1977 and 1992
- ▶ Outcomes
  - Cannabis use before age 17
  - Completion of high school and university degree by age 25
  - Cannabis dependence between ages 17–25
  - Use of other illicit drugs past month to past year by ages 23–25
  - Suicide attempts ages 17–25
  - Moderate or severe depression past week to past month ages 17–25
  - Welfare dependence ages 27–30
- ▶ Logistic regression models adjusted for 53 factors associated with cannabis use and adverse psychosocial outcomes

# Compared to those who had not used cannabis prior to age 17, those who used daily before age 17 were...

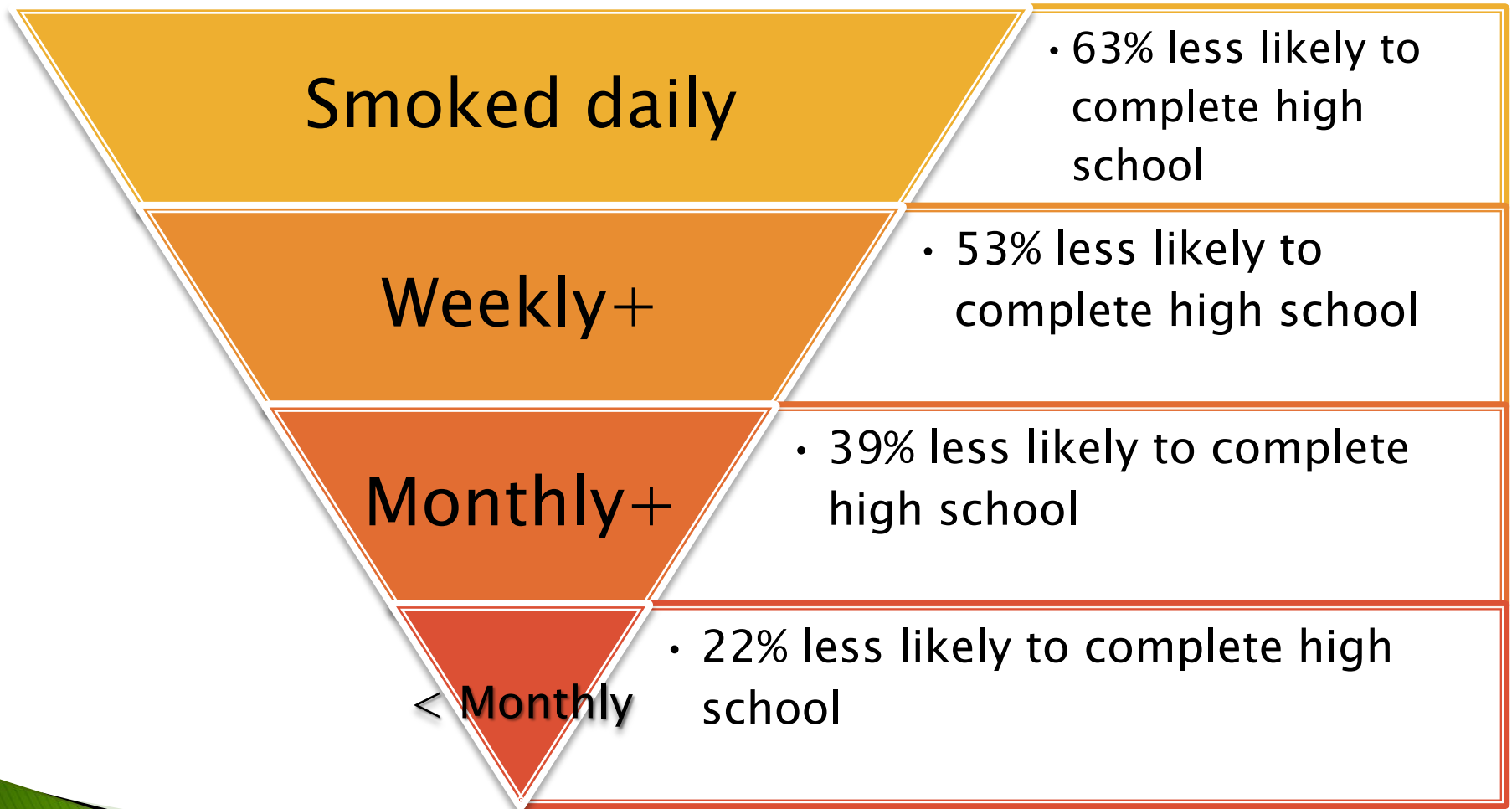
**Significantly more likely to...**

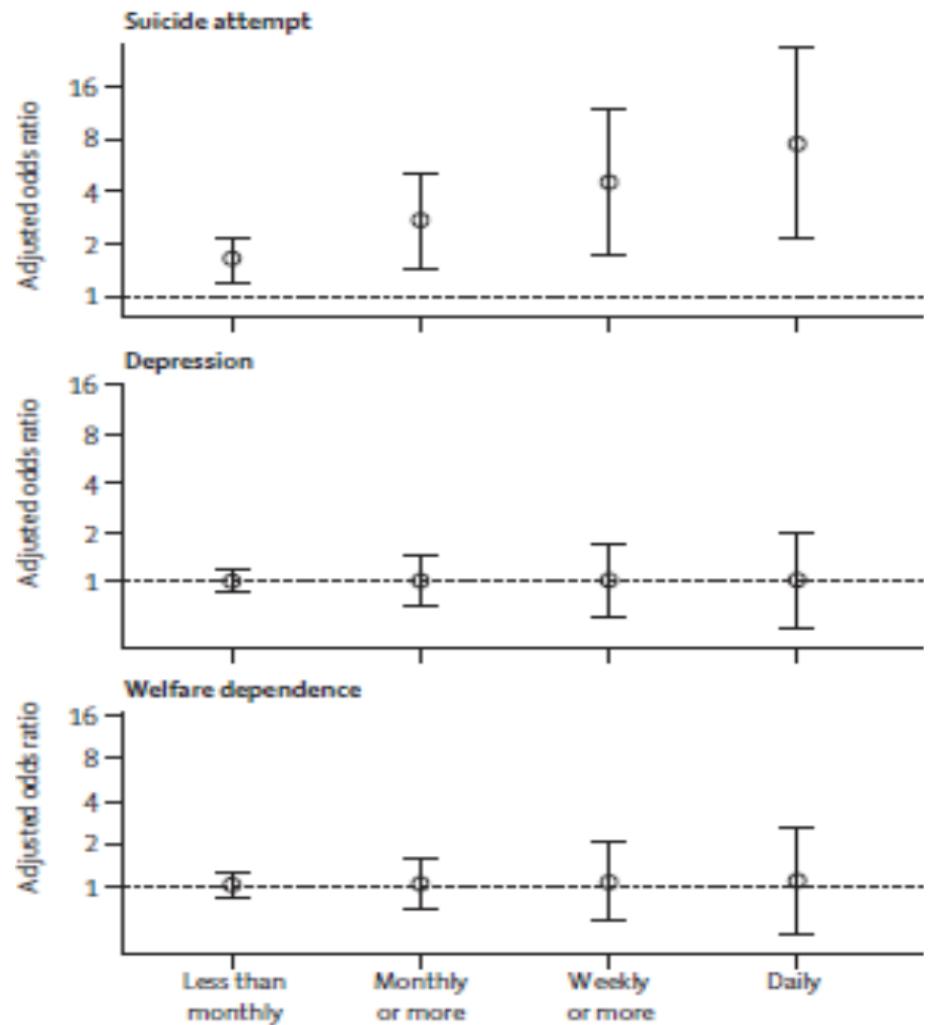
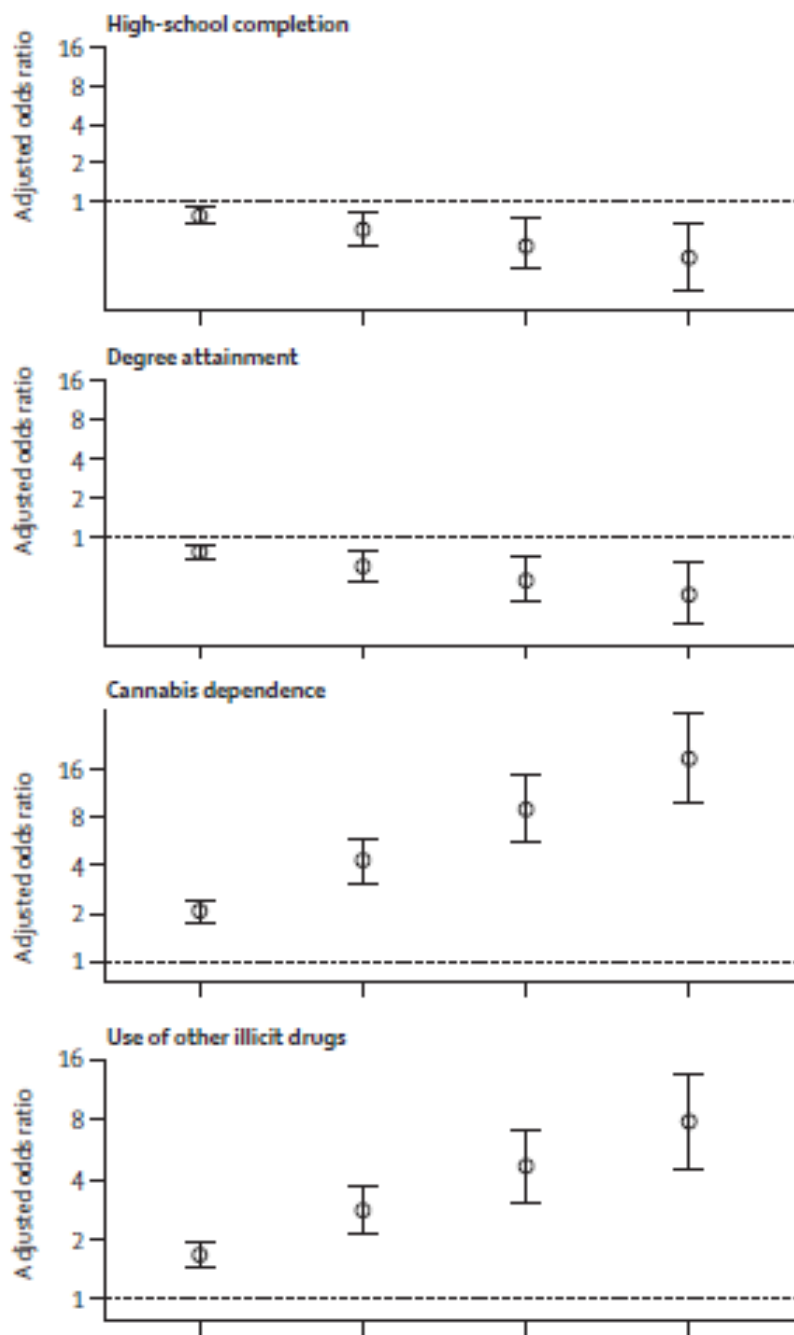
- Develop cannabis dependence (OR = 17.95)
- Report other illicit drug use (OR = 7.80)
- Attempt suicide (OR = 6.83)

**Significantly less likely to...**

- Complete high school (OR = .37)
- Obtain a college degree (OR = .38)

Similar results for those who used weekly+, monthly+, <monthly before age 17, but with increasingly smaller effects suggesting a dose-dependent relationship





Adjusted odds ratios (log scale) between maximum frequency of cannabis use before age 17 years and young adult outcomes in combined data, compared with individuals who have never used cannabis. Error bars show 95% CIs.



## Reply to Rogeberg and Daly: No evidence that socioeconomic status or personality differences confound the association between cannabis use and IQ decline

We reported that persistent cannabis use was associated with neuropsychological decline, from adolescence to midlife (1). Two commentators suggested alternative explanations; we tested these and report the results here.

Rogeberg (2) wonders whether socioeconomic differences explain the association between cannabis and neuropsychological decline. His argument is based on his assumption that cannabis use is more common in youngsters of low socioeconomic

persistent cannabis use and IQ decline that we reported ( $\beta = -0.152$ ;  $t = -4.45$ ;  $P < 0.0001$ ) remained unaltered ( $\beta = -0.158$ ;  $t = -4.58$ ;  $P < 0.0001$ ). We further restricted our analysis to study members who grew up in middle class families (whose breadwinners had occupations such as building inspector, aircraft mechanic), excluding low-SES families, as well as high-SES families (professional occupations such as dentist), thus precluding potential for low-SES confounding. The asso-

and IQ decline that we reported ( $\beta = -0.152$ ;  $t = -4.45$ ;  $P < 0.0001$ ) remained unaltered ( $\beta = -0.151$ ;  $t = -4.38$ ;  $P = 0.0001$ ). These tests exclude the possibility that the IQ drop is attributable to initial differences in conscientious personality.

Observational studies like ours cannot prove causation, and yet many important research questions, including whether cannabis alters cognitive function, are intractable to experimentation. It is unethical to

## Criticisms of the Meier et al. Dunedin cohort study from New Zealand >>>

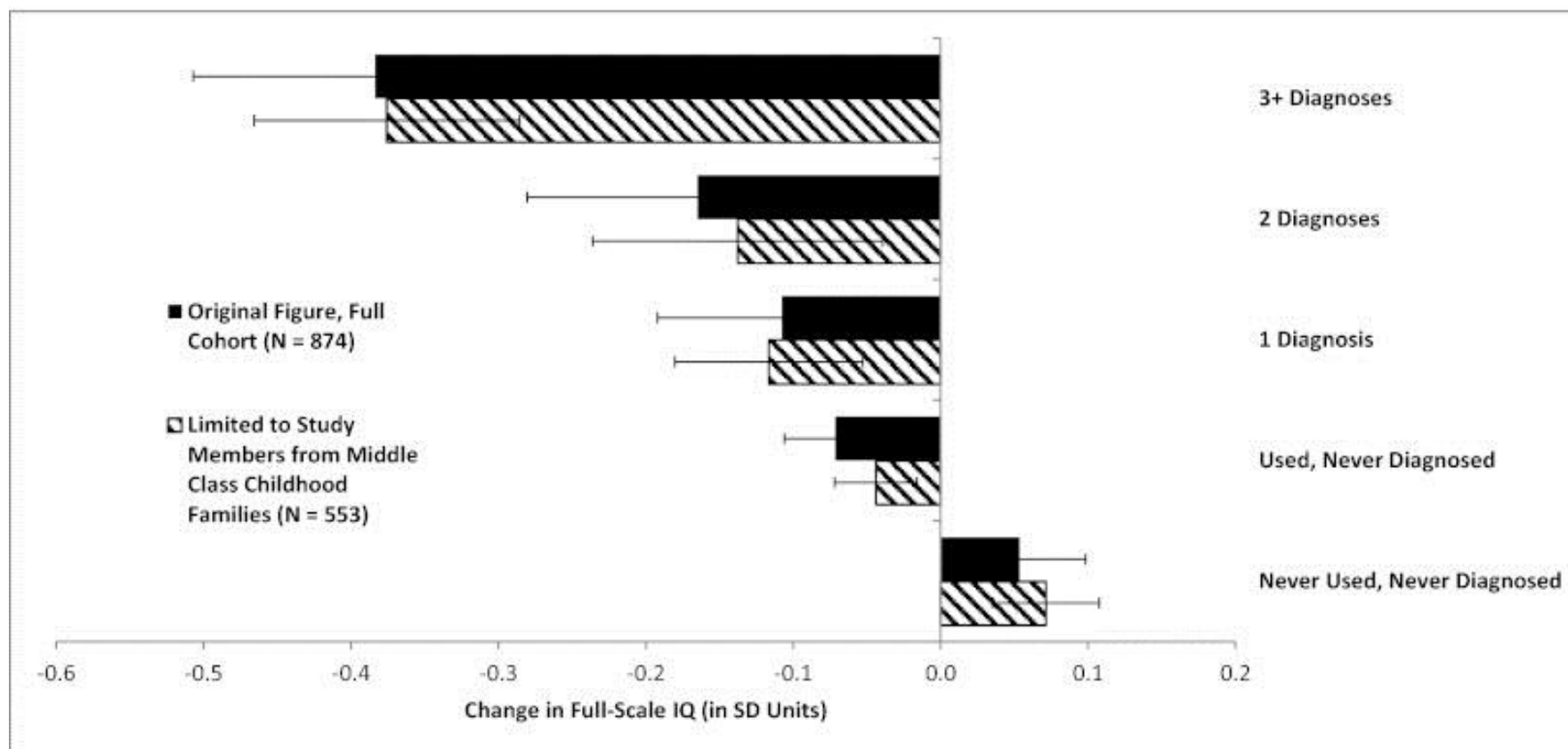
# Reply all but ruled out...

## Potential SES criticism

- Low SES did not predict adolescent-onset CUD
- IQs of individuals from low SES families did not decline from adolescence to adulthood and low SES unrelated to adolescent-to-adult IQ decline
- **Control for SES:** Association between CUD and neuropsych decline unchanged
  - Associations present when only middle class individuals were analyzed

## Potential conscientiousness criticism

- Measured by “childhood self control”, childhood conscientiousness unrelated to IQ decline
- **Control for childhood self-control:** Association between CUD and neuropsych decline unchanged



# Cannabis Use, Employment, and Income: Fixed-Effects Analysis of Panel Data

Ioana Popovici, PhD

Michael T. French, PhD

## Abstract

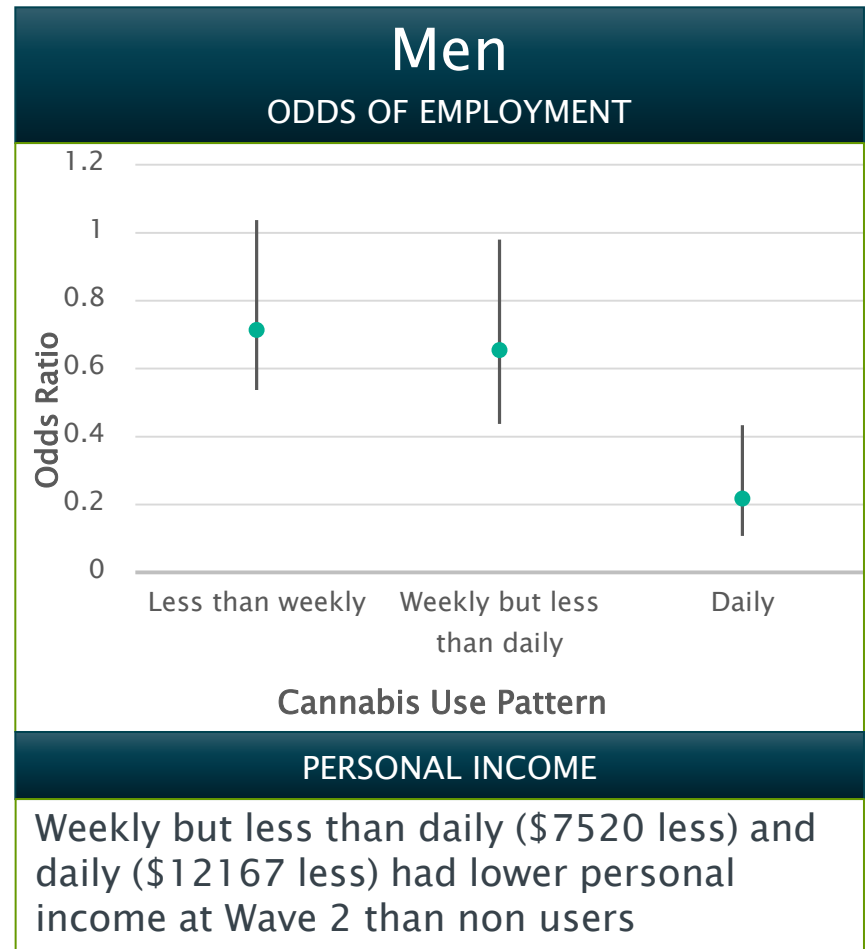
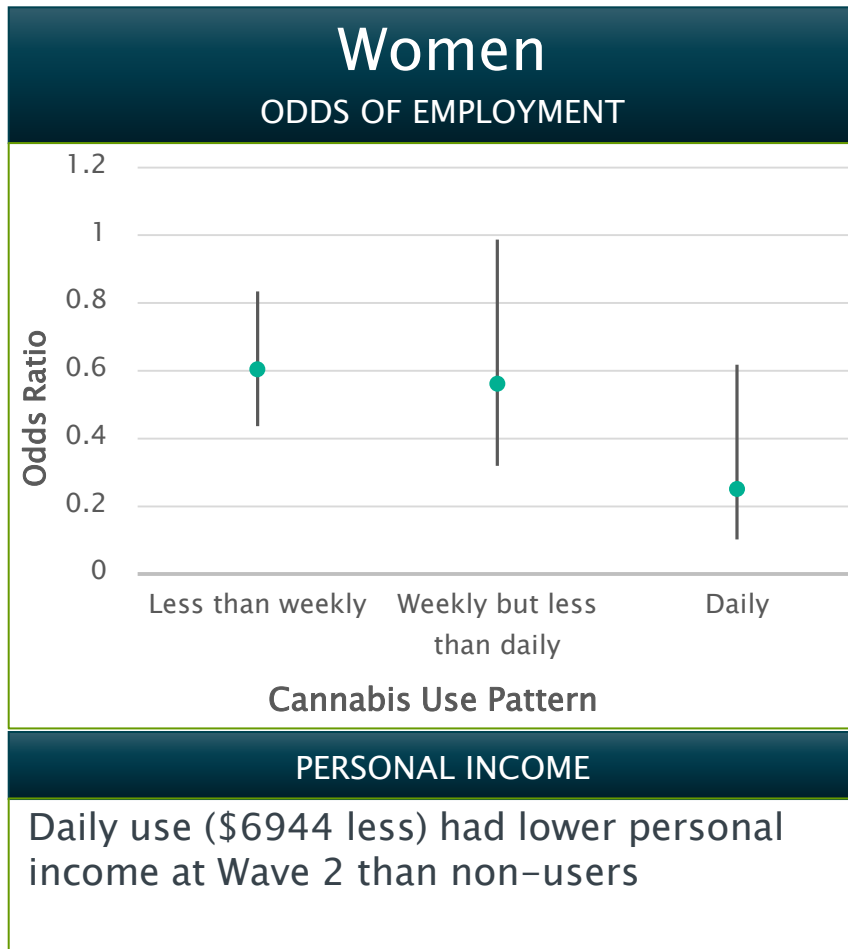
*Uncertainty exists regarding the direction and magnitude of the association between cannabis use and labor market outcomes. Using panel data from waves 1 and 2 of the National Epidemiological Survey of Alcohol and Related Conditions, the current paper estimates the associations between several patterns of cannabis use during the past year, current employment, and annual personal income. In the single-equation models (wave 2 data), nearly all patterns of cannabis use are significantly associated with worse labor market outcomes ( $p < 0.05$ ). However, when using fixed-effects techniques to address unobserved and time-invariant individual heterogeneity, the estimates are generally smaller in magnitude and less likely to be statistically significant vis-à-vis the benchmark estimates. These findings suggest that unobserved individual heterogeneity is an important source of bias in models of cannabis use and labor market outcomes. Moreover, cannabis use may be less detrimental in the labor market than other studies have reported.*

Effects of cannabis use on »»  
employment status and income

# Effects of cannabis use on employment status and income

- ▶ Longitudinal cohort design using National Epidemiological Survey on Alcohol and Related Conditions (NESARC), Waves 1 and 2 (2000–2001 and 2004–2005)
- ▶ 7077 women and 7199 men ages 21–60 at Wave 1
- ▶ Measures
  - Employment and income in past 12 months at Wave 2
  - Cannabis use (No cannabis use, Less than weekly, Weekly but less than daily, Daily)
  - CannabisUse Disorder past year
- ▶ Models adjusted for demographic characteristics, general and mental health status, binge drinking, cigarette smoking, other drug use status, and state differences in unemployment rates.

# Effects of cannabis use on employment status and income



**However,** when a fixed-effects technique removes unmeasured variability due to individual specific variables, all associations reduce to non-significance (ORs within 95% CI)

## Marijuana use trajectories during the post-college transition: Health outcomes in young adulthood

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### ABSTRACT

**Background:** Despite the relatively high prevalence of marijuana use among college students, little information exists regarding health outcomes associated with different use patterns or trajectories.

**Methods:** Seven annual personal interviews (Years 1–7) were administered to 1253 individuals, beginning in their first year in college. Growth mixture modeling was used to identify trajectories of marijuana, alcohol, and tobacco use frequency during Years 1–6. Logistic regression was used to evaluate the relationship between marijuana use trajectories and several Year 7 health outcomes, holding constant Year 1 health, demographics, and alcohol and tobacco use trajectories.

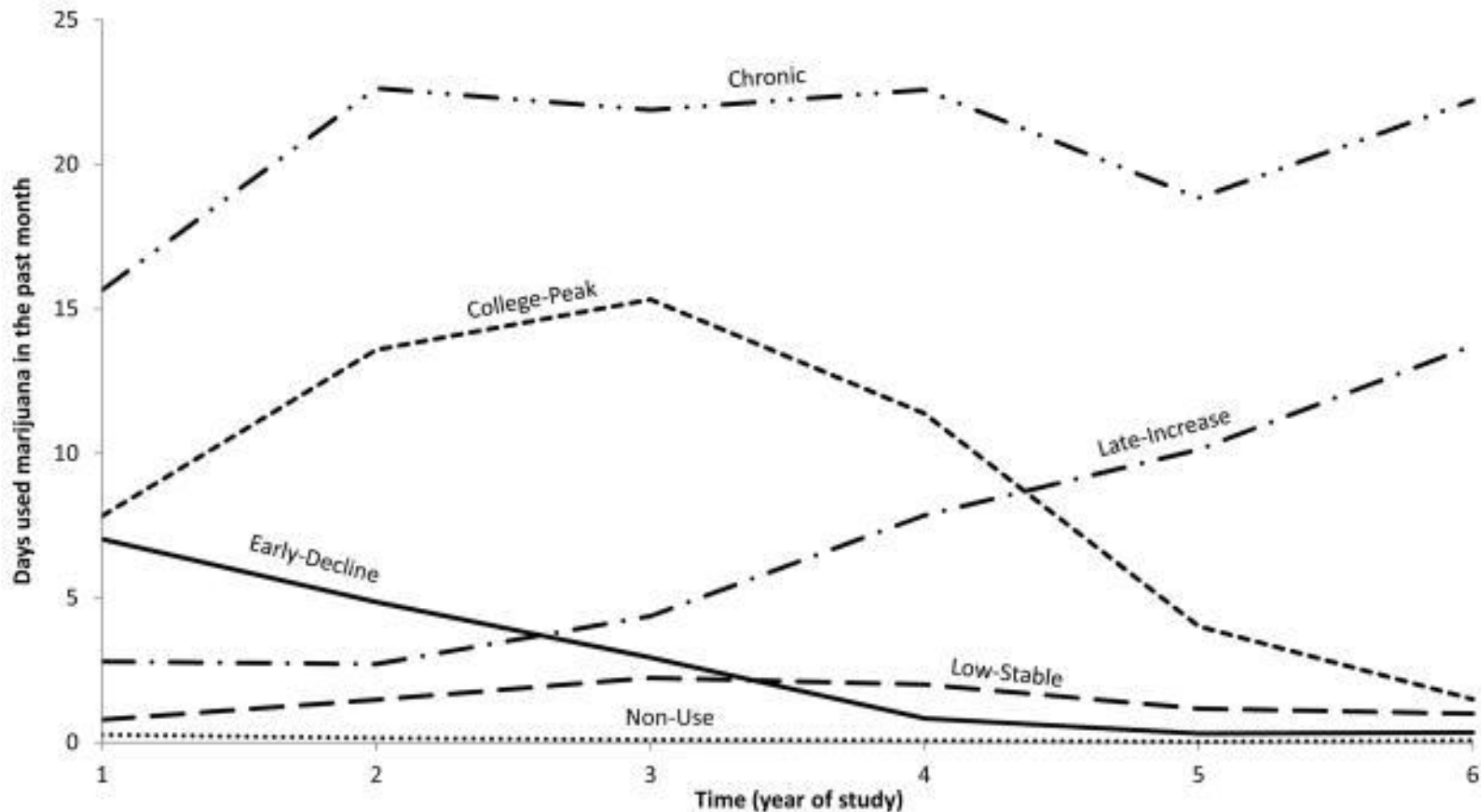
Effects of marijuana on health and mental health service utilization and outcomes »»

# Effects of marijuana on health and mental health service utilization and outcomes

- ▶ College Life Study at one large public university
- ▶ Measured upon college entry ( $N = 1253$ ; 608 men), ages 17–20 at baseline, annual follow-ups for 6 years
- ▶ Outcomes measured Y7 and marijuana use Y1–Y6 to establish temporal precedence between putative cause and effect
- ▶ Multiple regression using marijuana trajectory based on Y1–Y6 and Y7 outcomes adjusted for demographics, and Y1–Y6 alcohol and tobacco trajectory group membership, as well as Y1 values of the outcomes in each of their respective models (with General Health used for health utilization, impairment, and quality of life)

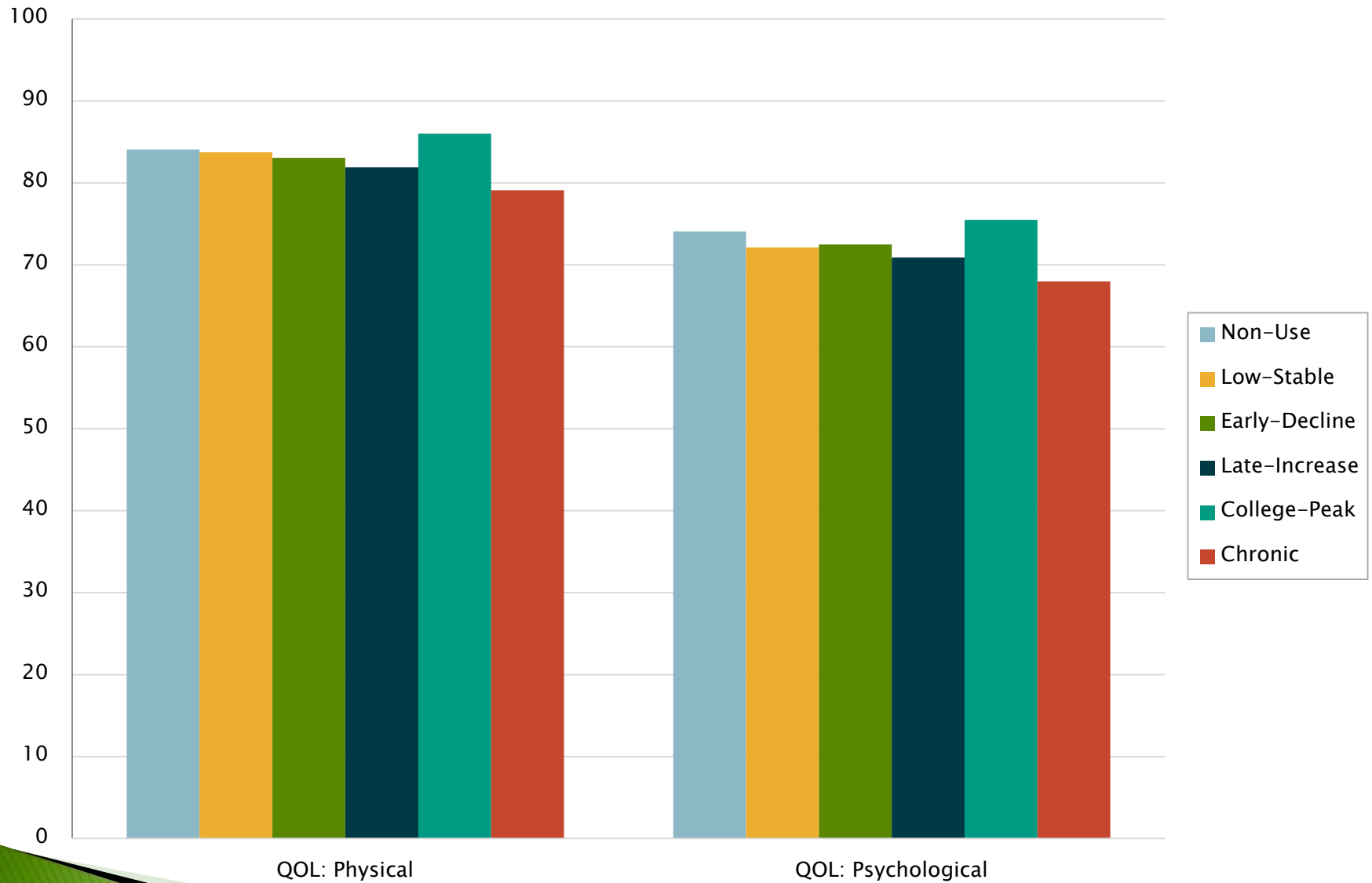
|  |               |     |
|--|---------------|-----|
| Six trajectories of marijuana use identified based on annual frequencies of past month use | Non-use       | 61% |
|  | Low-Stable    | 12% |
|  | Late-increase | 6%  |
|  | Early-Divide  | 7%  |
|  | College-Peak  | 8%  |
|  | Chronic       | 6%  |

Groups did not differ on any of the outcomes at baseline (Y1)



| Marijuana Trajectory Group | <i>n</i> | % of Sample | Weighted % | Marijuana Trajectory Group | <i>n</i> | % of Sample | Weighted % |
|----------------------------|----------|-------------|------------|----------------------------|----------|-------------|------------|
| Non-Use                    | 766      | 61.1        | 71.5       | Early-Divide               | 81       | 6.5         | 4.3        |
| Low-Stable                 | 154      | 12.3        | 10.0       | College-Peak               | 100      | 8.0         | 5.4        |
| Late-Increase              | 74       | 5.9         | 4.7        | Chronic                    | 78       | 6.2         | 4.2        |

## Year 7 Health Outcomes



## Worth the wait: effects of age of onset of marijuana use on white matter and impulsivity

Staci A. Gruber • Mary Kathryn Dahlgren •  
Kelly A. Sagar • Atilla Gönenç • Scott E. Lukas

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### Abstract

**Rationale** Marijuana (MJ) use continues to rise, and as the perceived risk of using MJ approaches an all-time historic low, initiation of MJ use is occurring at even younger ages. As adolescence is a critical period of neuromaturation, teens and

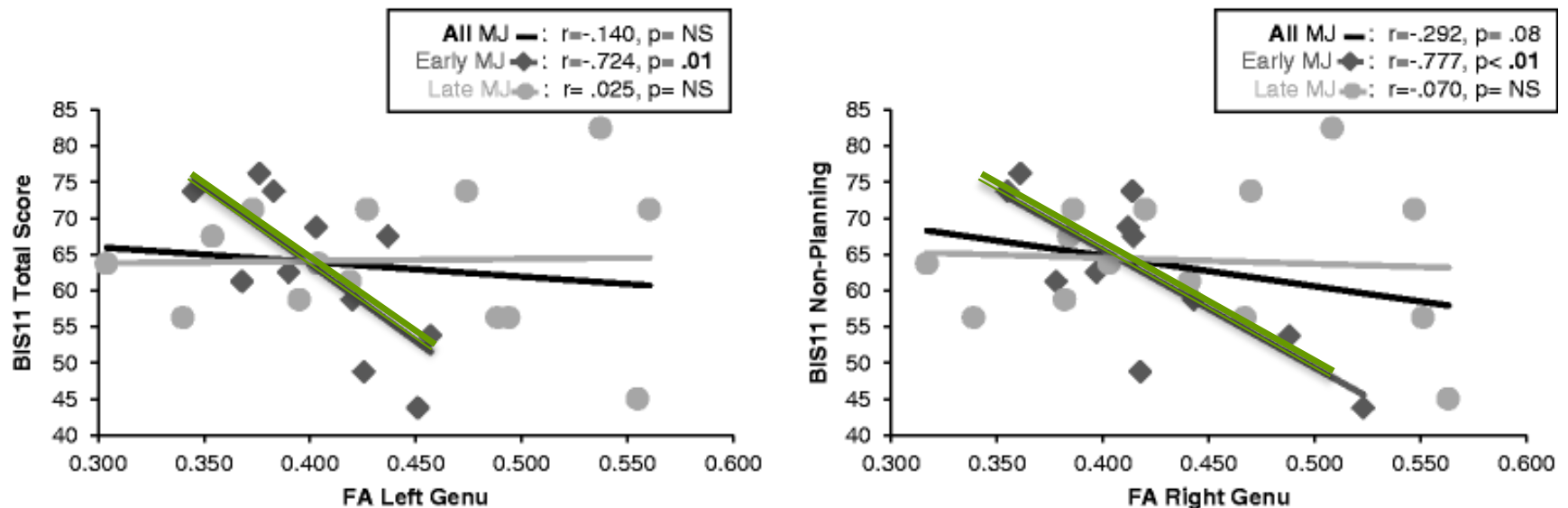
levels of FA. Interestingly, within the early onset group, higher impulsivity scores were correlated with lower FA, a relationship that was not observed in the late onset smokers. **Conclusions** MJ use is associated with white matter development and reported impulsivity, particularly in early

White matter in the brain and impulsivity »»  
in young marijuana users

# Effects of cannabis on white matter in the brain and impulsivity moderated by age of onset

- ▶ Cross-sectional neuroimaging study using diffusion tensor imaging (DTI)
- ▶ 25 individuals with cannabis use disorder (CUD) vs. 18 healthy controls
  - CUD group smoked 2500+ times, used cannabis at least 5 of past 7 days, positive urine screen for cannabinoids;
  - Co-occurring disorders excluded
  - Matched on age, IQ, alcohol and cigarette use, SES, personality factors
- ▶ Early onset defined as age beginning regular use (n=11: <16 years, n=14: 16+ years)
  - Early onset CUD smoked more often and twice as much cannabis each week
  - Impulsivity measured by Barratt Impulsivity Scale: attention, motor, non planning scales

# Effects of cannabis on white matter in the brain and impulsivity moderated by age of onset



- CUD more impulsive than controls on all three subscales and total score
- Fractional anisotropy (white matter measure) reduced in the corpus callosum for CUD group
- White matter positively correlated with age of onset
  - Later onset related to better connectivity
- Relationship between lower levels of fractional anisotropy and impulsivity moderated by age of onset:
  - Weak overall relationships, but strong relationship for early onset smokers ( $r_s = .7$ )
  - No relationships among late onset smokers ( $r_s = 0$ )

## Impact of Marijuana on Response Inhibition: An fMRI Study in Young Adults

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Received June 26, 2011; revised July 19, 2011; accepted August 4, 2011

### Abstract

**Rationale:** Marijuana use in adolescence is prevalent and increasing. Understanding the neural correlates of the impact of this use is critical for policy making and for youth awareness. **Objectives:** The effects of marijuana use on response inhibition were investigated in 19 - 21-year-olds using functional magnetic resonance imaging (fMRI). **Methods:** Participants were members of the Ottawa Prenatal Prospective Study, a longitudinal study that collected a unique body of information on participants from infancy to young adulthood including: prenatal drug history, detailed cognitive/behavioral performance, and current and past drug use. This information allowed for the control of an unparalleled number of potentially confounding variables including: prenatal marijuana, nicotine, alcohol, and caffeine exposure and offspring alcohol, marijuana, and nicotine use. Ten marijuana users and 14 nonusers that served as controls performed a Go/No-Go task while fMRI blood oxygen level-dependent response was examined. **Results:** Despite similar task performance, there was a positive relationship between amount of marijuana smoked and activation in right thalamus, premotor cortex and middle frontal gyrus. These regions form part of the neural network responsible for inhibition control. There was also a positive dose dependent relationship with marijuana and activation in inferior parietal lobe and precuneus, also parts of response inhibition pathways. **Conclusions:** These results suggest a dose dependent alteration in neural functioning during response inhibition after controlling for other prenatal and current drug use. These alterations may be necessary in order to compensate for neural changes in response inhibition circuits caused by long term marijuana use that began during adolescence/young adulthood.

**Keywords:** Prefrontal Cortex, fMRI, Marijuana, Young Adulthood, Response Inhibition

### 1. Introduction

Research has demonstrated that the inability to successfully monitor and inhibit inappropriate behaviours is apparent in substance abusers as well as in other individuals with altered frontal neural circuitry [1]. Such disruption in executive functioning, which can also include selective attention and short term storage of information, initiation of response to relevant information and self-monitoring of performance in order to achieve a desired goal [1], can cause severe disruption in daily life. Of these elements, however, response inhibition is most vital since it allows for successful adaptation to the environment,

recognizing unexpected situations, making plans and changing behaviour accordingly.

Functional magnetic resonance imaging (fMRI) research has shown that response inhibition is mediated by a wide neural network that involves the frontal lobes as well as circuits connecting the frontal lobes with other regions such as the parietal lobes, cerebellum, striatum and thalamus [2-3]. Other observed regions include the premotor area, the supplementary motor area, the dorso-lateral and orbitofrontal areas and the anterior cingulate cortex [4].

The 2011 Monitoring the Future Survey reported that there is an increase in American youth marijuana use and

## Effects of marijuana on visuospatial working memory: an fMRI study in young adults

Andra M. Smith · Carmelinda A. Longo ·

Peter A. Fried · Matthew J. Hogan · Ian Cameron

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© Springer-Verlag 2010

### Abstract

**Objectives** The effects of marijuana use on visuospatial working memory were investigated in 19–21-year-olds using functional magnetic resonance imaging (fMRI).

**Methods** Participants were members of the Ottawa Prenatal Prospective Study, a longitudinal study that collected a unique body of information on participants from infancy to young adulthood including: prenatal drug history, detailed cognitive/behavioral performance, and current and past drug use. This information allowed for the measurement of an unprecedented number of potentially confounding drug exposure variables including: prenatal marijuana, nicotine, alcohol, and caffeine exposure and offspring alcohol, marijuana, and nicotine use. Ten marijuana users and 14 nonusing controls performed a visuospatial 2-back task while fMRI blood oxygen level-dependent response was examined.

**Results** Despite similar task performance, marijuana users had significantly greater activation in the inferior and middle frontal gyri, regions of the brain normally associated with visuospatial working memory. Marijuana users also

had greater activation in the right superior temporal gyrus, a region of the brain not typically associated with visuospatial working memory tasks.

**Conclusions** These results suggest that marijuana use leads to altered neural functioning during visuospatial working memory after controlling for other prenatal and current drug use. This alteration appears to be compensated for by the recruitment of blood flow in additional brain regions. It is possible that this compensation may not be sufficient in more real-life situations where this type of processing is required and thus deficits may be observed. Awareness of these neural physiological effects of marijuana in youth is critical.

**Keywords** Visuospatial working memory · Marijuana · Executive functioning · Functional magnetic resonance imaging

### Introduction

Marijuana continues to be the most commonly used illegal drug in the world, with almost 160 million people, aged 15–64, reporting having used marijuana in the last year (World Drug Report 2007). Although the marijuana plant contains several hundred compounds, its most psychoactive ingredient is THC or delta-9-tetrahydrocannabinol (Mechoulam and Gaoni 1967). Research has found that THC binds to CB1 receptors, which are located in various concentrations throughout the brain, with high densities found in the frontal regions of the cerebral cortex and in the hippocampus (Devane et al. 1988; Herkenham et al. 1990). The frontal cortex is responsible for executive functioning processes such as decision making, planning, problem solving, focused attention, response inhibition, cognitive

Neurobiological functioning of young marijuana users on response inhibition and working memory tasks >>>

# Neurobiological functioning of young marijuana users on response inhibition and working memory tasks

- ▶ Two cross-sectional studies using fMRI from young adults in the Ottawa Prenatal Prospective Study
- ▶ 10 cannabis users and 14 non-using controls, ages 19–21
  - No differences on personality factors, psychiatric disorder (apart from CUD), SES, Conners' Parent Rating Scale of behavior.
  - Potentially meaningful differences (not statistically significant):
    - Higher verbal IQ among non-users (117 vs. 106,  $M=100$ ,  $SD=15$ )
    - Greater extraversion among non-users (59 vs. 50,  $M=50$ ,  $SD=10$ )
  - Differences on alcohol and cigarette smoking controlled for statistically
  - No other drugs of misuse, no parent DSM-IV diagnosis
- ▶ Measures:
  - Visuospatial working memory: measured by the N-Back task
  - Motor response inhibition: measured by the Go/No-Go task
  - fMRI completed while individuals performed the tasks

# Neurobiological functioning of young marijuana users on response inhibition and working memory tasks

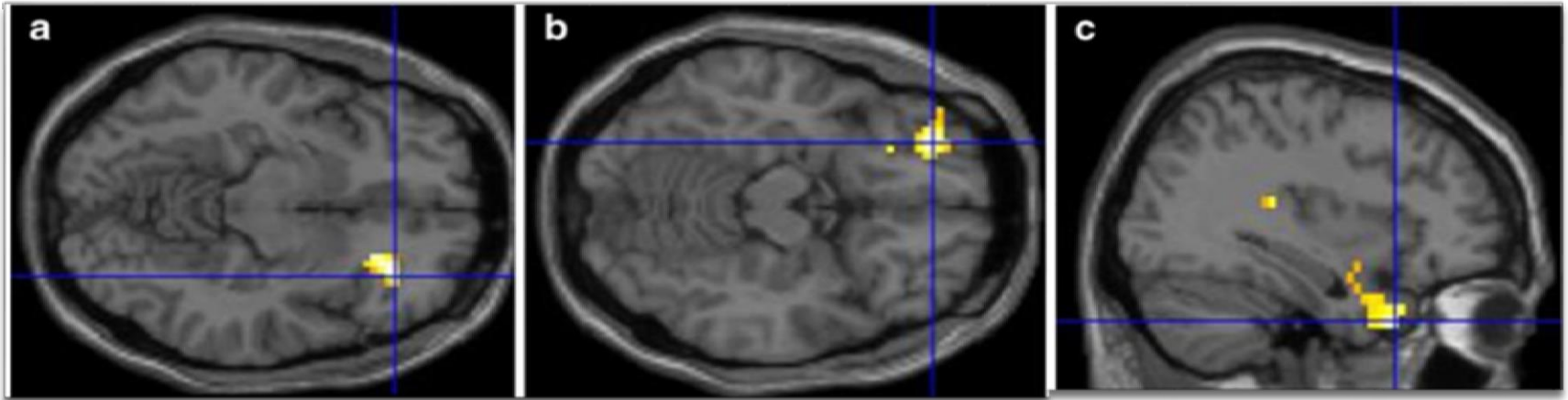
## Working Memory

- No significant differences on N-Back task
- Cannabis users: greater activation on areas of the frontal gyri indicated in visuospatial processing,
  - Brodmann areas 11 (orbitofrontal) and 38 (temporopolar)

## Response Inhibition

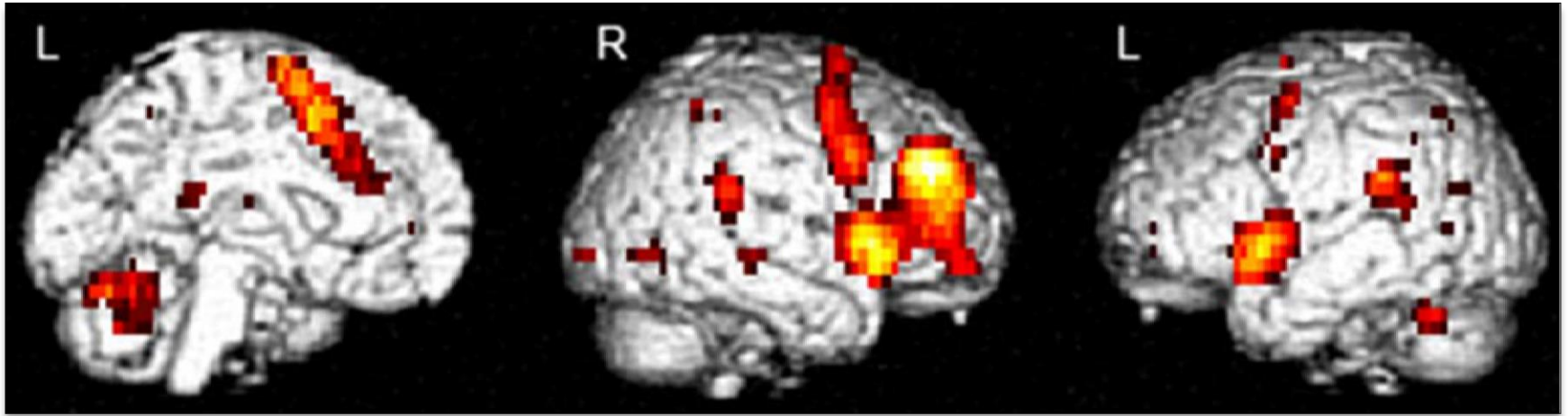
- No significant differences on Go/No-Go task
- Differences between activation for the “Press all letters except for X” (Response inhibition task) minus “Rest” activation in a dose-response relationship
  - More marijuana use → greater activation in areas of the premotor cortex, right thalamus, and right middle frontal gyrus

# Activation differences between Cannabis Users and Non-Users



## Working Memory Task

# Activation differences between Cannabis Users and Non-Users



## Response Inhibition Task

# Cannabis as a risk factor for psychosis: systematic review

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Andrew M. McIntosh *Division of Psychiatry, University of Edinburgh, Edinburgh, UK.*

Stephen M. Lawrie *Division of Psychiatry, University of Edinburgh, Edinburgh, UK.*

## Abstract

Various lines of evidence suggest an association between cannabis and psychosis. Five years ago, the only significant case-control study addressing this question was the Swedish Conscript Cohort. Within the last few years, other studies have emerged, allowing the evidence for cannabis as a risk factor to be more systematically reviewed and

psychosis. Seven were included in the meta-analysis, with a derived odds ratio (fixed effects) of 2.9 (95% confidence interval = 2.4–3.6). No evidence of publication bias or heterogeneity was found. Early use of cannabis did appear to increase the risk of psychosis. For psychotic symptoms, a dose-related effect of cannabis use was seen, with

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CA and New Delhi  
10.1177/0269881105049040

## Effects of marijuana use on psychosis »»

| Study                           | Sample size (n)                            | Age range (years)                    | Unadjusted odds ratio (OR)   | Population studied   | Cannabis use criteria  | Criteria for psychotic symptoms  |
|---------------------------------|--|--------------------------------------|--|--|--|--|
| Tien and Anthony (1990)         | 4994                                       | 18–49 years                          | 2.62   | US National Institute of Mental Health (NIMH) Epidemiological Catchment Area Program: household survey | Self-reported daily use of cannabis  | 'Self-reported psychotic experiences' (1 or more positive responses from 12 items of the Diagnostic Interview Schedule (DIS) relating to delusions and hallucinations)                   |
| Degenhardt <i>et al.</i> (2001) | 10641                                      | 18–35+ years                         | 3.56 (use)<br>4.64 (abuse)<br>10.80 (dependence)   | Australian National Survey of Mental Health and Well-Being (NSMHWB)                                    | 'No use': less than 6 occasions in last year<br>'Use': more frequent, but not meeting DSM-IV criteria<br>'cannabis abuse' DSM-IV criteria for<br>'cannabis dependence' | Score of 3 or more on 'psychosis screener' comprising delusions of control, interference and passivity, delusions of reference, persecution, and grandiose delusions                     |
| Degenhardt and Hall (2001)      | 6722                                       | Under 50 years                       | 3.98 (use)<br>4.15 (weekly use)<br>5.86 (disorder)   | Subset of NSMHWB dataset   | 'Cannabis use': undefined<br>'Weekly cannabis use'<br>'Cannabis use disorder': meeting any DSM-IV 'disorder' criteria  | Score of 3 or more on 'psychosis screener' comprising 7 items: delusions of control, thought interference and passivity, delusions of reference and persecution, and grandiose delusions |
| Fergusson <i>et al.</i> (2003)  | 1025 (age 18 years)<br>1011 (age 21 years) | Data gathered at age 18 and 21 years | 'Rate ratio' for mean psychotic symptoms:<br>3.7 (age 18 years)<br>2.3 (age 21 years)<br>1.8 (adjusted for confounds, including previous symptoms) | New Zealand birth cohort: the Christchurch Health and Development Study (CHDS)                         | DSM-IV criteria for 'cannabis dependence' derived from the Composite International Diagnostic Interview (CIDI)   | Total number of 'psychotic symptoms' in past 12 months from the SCL-90-R Checklist 90 (SCL-90-R)   |

Largest cross-sectional of a general population, found possible dose-related effect

Higher rate ratio for psychotic symptoms at age 18 than age 21

## Case control studies of reported psychotic symptoms and cannabis use

| Study                         | Sample size (n) | Age range (years) | Unadjusted odds ratio (OR)  | Population studied  | Nature of 'high risk' status  | Follow-up period                            | Cannabis use criteria  | 'Psychosis' criteria   |
|-------------------------------|-----------------|-------------------|---|---|---|---|--|--|
| Miller <i>et al.</i> (2001)   | 191             | 16–25 years       | Current use:<br><i>Occasional</i> :<br>1.3 (0.5–3.1)<br><i>Frequent</i> :<br>7.4 (2.4–22.6)<br>Past use:<br><i>Occasional</i> :<br>1.0 (0.5–2.2)<br><i>Frequent</i> :<br>6.1 (2.1–17.6) | Edinburgh High Risk Study: 155 'high risk' subjects and 36 matched controls | No previous diagnosis of serious psychiatric disorder. At least 2 first- or second-degree relatives who suffered from schizophrenia                                 | Data for 'at entry' psychotic symptoms only | Structured interview for 'cannabis use' past and current: none, occasional, frequent                                 | Present State Examination (PSE): evidence of delusions, hallucinations, or other behaviours, not sufficiently severe to meet the criteria for schizophrenic or related psychotic illness       |
| Phillips <i>et al.</i> (2002) | 100             | 14–28 years       | 1.43 (0.6–3.41) (non-significant)   | Australian 'ultra' high risk cohort   | 3 groups (combined):<br>'Trait and State Risk Factor Group'*<br>'Attenuated Psychotic Symptoms Group'**<br>'Brief Limited Intermittent Psychotic Symptoms Group'*** | 12 months                                   | DSM-IV criteria for 'cannabis dependence' assessed using Schedules for clinical assessment in neuropsychiatry (SCAN) | BPRS: a least one significant score for hallucinations, delusions, paranoia, or formal thought disorder; held with strong conviction (3+ on CASH); daily frequency; lasting longer than 1 week |

Found cannabis to be independent risk factor for presence of psychotic symptoms, with possible dose-related effect

Did not find an increased risk

\*First-degree relative with a psychotic disorder or presence of schizotypal personality disorder and recent functional decline; \*\*Presence of subthreshold psychotic symptoms; \*\*\*Episode(s) of frank psychosis lasting less than 1 week and spontaneously abated

# Studies of high risk groups, cannabis use, and psychotic symptoms

# Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study

Louise Arseneault, Mary Cannon, Richie Poulton, Robin Murray, Avshalom Caspi, Terrie E Moffitt

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*Editorial by Rey and Tennant  
Papers pp 1195, 1199*

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*professor*

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College

The strongest evidence that cannabis use may be a risk factor for later psychosis comes from a Swedish cohort study which found that heavy cannabis use at age 18 increased the risk of later schizophrenia sixfold.<sup>1 2</sup> This study could not establish whether adolescent cannabis use was a consequence of pre-existing psychotic symptoms rather than a cause. We present the first prospective longitudinal study of adolescent cannabis use as a risk factor for adult schizophreniform disorder, taking into account childhood psychotic symptoms<sup>3</sup> antedating cannabis use.

## Methods and results

The Dunedin multidisciplinary health and development study (a study of a general population birth cohort of 1037 individuals born in Dunedin, New Zea-

We divided the sample into three groups based on cannabis use at ages 15 and 18. The 494 controls (65.1% of the sample) had reported using cannabis “never” or “once or twice” at both ages; cannabis users by age 18 (236; 31.1%) first reported using cannabis “three times or more” at age 18; and cannabis users by age 15 (29; 3.8%) had reported using cannabis “three times or more” at age 15 (all of whom continued to use cannabis at age 18).

Psychiatric outcomes at age 26 were symptoms of schizophrenia and depression and diagnoses of schizophreniform disorder and depression.

Multiple linear regression analyses showed that cannabis users by age 15 and by age 18 had more schizophrenia symptoms than controls at age 26 (table). These results remained significant after psychotic symptoms at age 11 were controlled for. The

## Dunedin Birth Cohort Study >>

Found that even when psychotic symptoms at age 11 years were controlled for, cannabis users by age 15 years and by age 18 years had significantly more ‘schizophrenia symptoms’ compared to controls

|        |                                     | Schizophrenia outcomes                  |         |   |         |
|--------|-------------------------------------|---|---------|---|---------|
| Model* | Predictor                           | Schizophrenia symptoms<br>(scores 0-58) |         | Schizophreniform disorder<br>(n=25; 3.3%) |         |
|        |                                     | B $\Uparrow$ (SE)                       | P value | Odds ratio (95% CI)                       | P value |
| 1†     | Cannabis users by age 15            | 6.91 (0.91)                             | 0.001   | 4.50 (1.11 to 18.21)                      | 0.035   |
|        | Cannabis users by age 18            | 1.04 (0.40)                             | 0.009   | 1.65 (0.65 to 4.18)                       | 0.293   |
| 2‡     | Weak psychotic symptoms at age 11   | 0.68 (0.53)                             | 0.201   | 4.65 (1.84 to 11.78)                      | 0.001   |
|        | Strong psychotic symptoms at age 11 | 5.16 (1.39)                             | 0.001   | 15.97 (3.38 to 75.47)                     | 0.001   |
|        | Cannabis users by age 15            | 6.56 (0.91)                             | 0.001   | 3.12 (0.73 to 13.29)                      | 0.124   |
|        | Cannabis users by age 18            | 1.03 (0.39)                             | 0.009   | 1.42 (0.54 to 3.74)                       | 0.473   |
| 3§     | Other drug users at age 15 to 18    | -0.3 (0.69)                             | 0.615   | 0.30 (0.05 to 1.62)                       | 0.160   |
|        | Cannabis users by age 15            | 7.2 (1.07)                              | 0.001   | 11.38 (1.84 to 70.45)                     | 0.009   |
|        | Cannabis users by age 18            | 1.1 (0.42)                              | 0.008   | 1.95 (0.76 to 5.01)                       | 0.167   |

## Dunedin Birth Cohort Study

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# Confirmation that the *AKT1* (rs2494732) Genotype Influences the Risk of Psychosis in Cannabis Users

Marta Di Forti, Conrad Iyegbe, Hannah Sallis, Anna Kolliakou, M. Aurora Falcone, Alessandra Paparelli, Miriam Sirianni, Caterina La Cascia, Simona A. Stilo, Tiago Reis Marques, Rowena Handley, Valeria Mondelli, Paola Dazzan, Carmine Pariante, Anthony S. David, Craig Morgan, John Powell, and Robin M. Murray

**Background:** Cannabis use is associated with an increased risk of psychosis. One study has suggested that genetic variation in the *AKT1* gene might influence this effect.

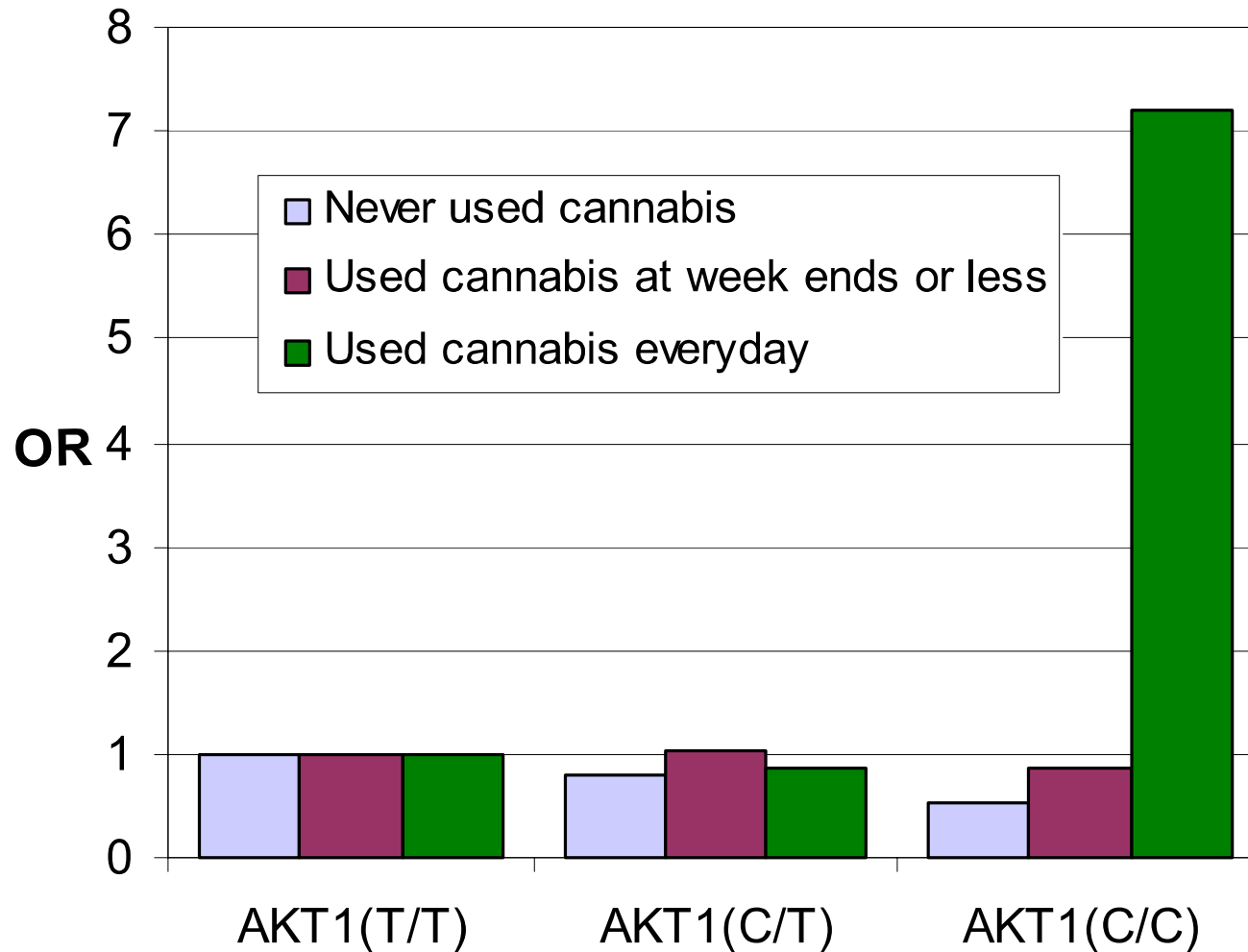
**Methods:** In a case-control study of 489 first-episode psychosis patients and 278 control subjects, we investigated the interaction between variation at the *AKT1* rs2494732 single nucleotide polymorphism and cannabis use in increasing the risk of psychosis.

**Results:** The rs2494732 locus was not associated with an increased risk of a psychotic disorder, with lifetime cannabis use, or with frequency of use. We did, however, find that the effect of lifetime cannabis use on risk of psychosis was significantly influenced by the rs2494732 locus (likelihood ratio statistic for the interaction = 8.54;  $p = .014$ ). Carriers of the C/C genotype with a history of cannabis use showed a greater than twofold increased likelihood of a psychotic disorder (odds ratio = 2.18 [95% confidence interval: 1.12, 4.31]) when compared with users who were T/T carriers. Moreover, the interaction between the rs2494732 genotype and frequency of use was also significant at the 5% level (likelihood ratio = 13.39;  $p = .010$ ). Among daily users, C/C carriers demonstrated a sevenfold increase in the odds of psychosis compared with T/T carriers (odds ratio = 7.23 [95% confidence interval: 1.37, 38.12]).

**Conclusions:** Our findings provide strong support for the initial report that genetic variation at rs2494732 of *AKT1* influences the risk of developing a psychotic disorder in cannabis users.

Whether adolescent marijuana use can contribute to developing psychosis later in adulthood may depend on existing genetically based vulnerability >>

# AKT1 Gene Variants and Psychosis



- Daily users with C/C variant have seven times higher risk of developing psychosis than infrequent marijuana users or nonusers
- Risk for users with T/T variant unaffected by marijuana use

# Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction

Avshalom Caspi, Terrie E. Moffitt, Mary Cannon, Joseph McClay, Robin Murray, HonaLee Harrington, Alan Taylor, Louise Arseneault, Ben Williams, Antony Braithwaite, Richie Poulton, and Ian W. Craig

**Background:** Recent evidence documents that cannabis use by young people is a modest statistical risk factor for psychotic symptoms in adulthood, such as hallucinations and delusions, as well as clinically significant schizophrenia. The vast majority of cannabis users do not develop psychosis, however, prompting us to hypothesize that some people are genetically vulnerable to the deleterious effects of cannabis.

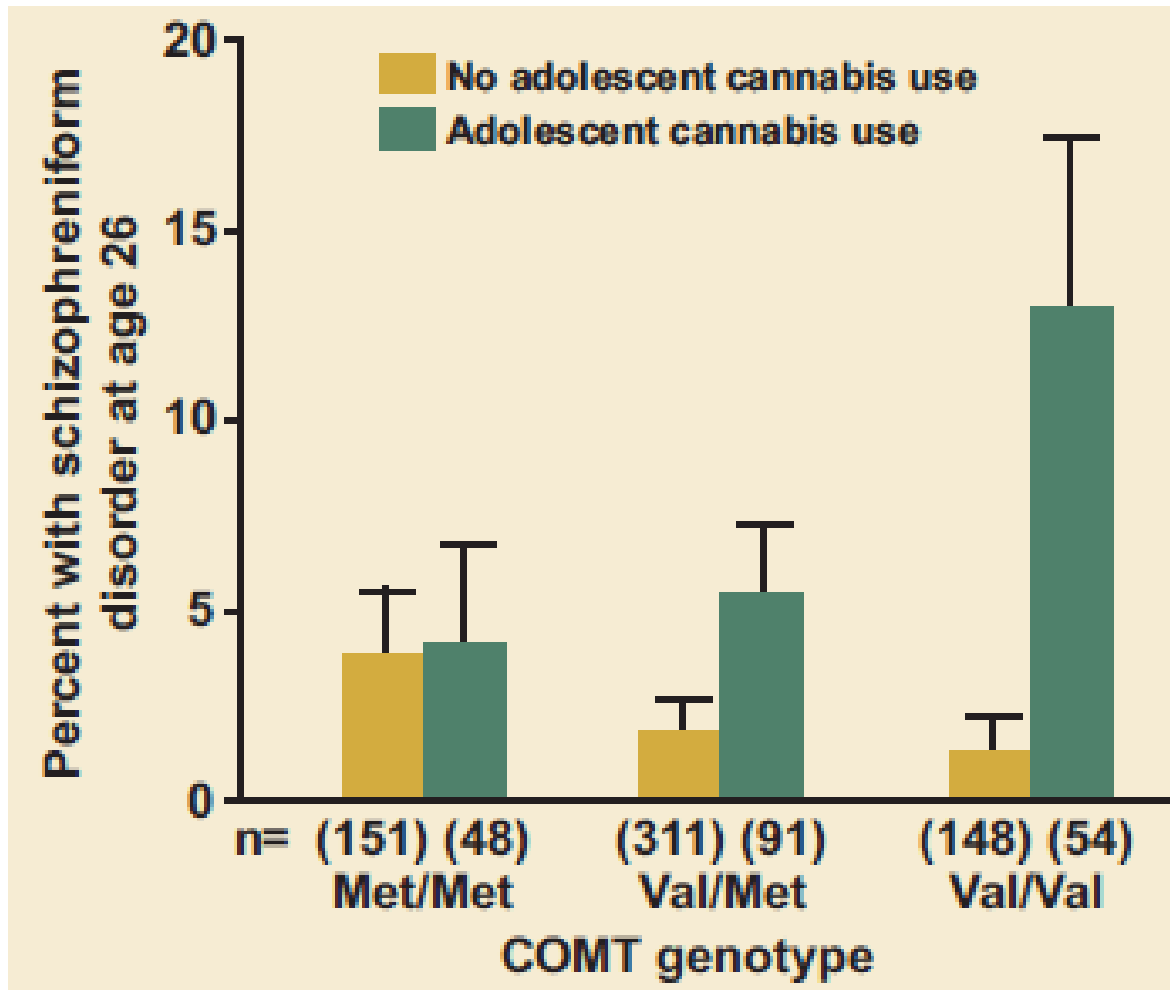
**Methods:** In a longitudinal study of a representative birth cohort followed to adulthood, we tested why cannabis use is associated with the emergence of psychosis in a minority of users, but not in others.

**Results:** A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis. Carriers of the COMT valine<sup>158</sup> allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis use had no such adverse influence on individuals with two copies of the methionine allele.

**Conclusions:** These findings provide evidence of a gene  $\times$  environment interaction and suggest that a role of some susceptibility genes is to influence vulnerability to environmental pathogens.

Influence of adolescent marijuana use on adult psychosis is affected by genetic variables >>

# Influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene



- Individuals with copies of the Val variant have a higher risk of developing schizophrenic-type disorders if they used cannabis during adolescence
- Those with only the Met variant were unaffected by cannabis use.

# Additional Reviews

Review

## Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review

Nora D. Volkow, MD; James M. Swanson, PhD; A. Eden Evins, MD; Lynn E. DeLisi, MD; Madeline H. Meier, PhD; Raul Gonzalez, PhD; Michael A. P. Bloomfield, MRCPsych; H. Valerie Curran, PhD; Ruben Baler, PhD

With a political debate about the potential risks and benefits of cannabis use as a backdrop, the wave of legalization and liberalization initiatives continues to spread. Four states (Colorado, Washington, Oregon, and Alaska) and the District of Columbia have passed laws that legalized cannabis for recreational use by adults, and 23 others plus the District of Columbia now regulate cannabis use for medical purposes. These policy changes could trigger a broad range of unintended consequences, with profound and lasting implications for the health and social systems in our country. Cannabis use is emerging as one among many interacting factors that can affect brain development and mental function. To inform the political discourse with scientific evidence, the literature was reviewed to identify what is known and not known about the effects of cannabis use on human behavior, including cognition, motivation, and psychosis.

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Nora D. Volkow, MD, National Institute on Drug Abuse, National Institutes of Health

“Taken together, these findings highlight the need for longitudinal studies that follow-up adolescents from before to after initiation of cannabis use and combine neuropsychological testing with neuroimaging. The Adolescent Brain Cognitive Development Study, a large prospective National Institutes of Health-funded investigation of children ages 9 to 10 years who will be followed up for at least 10 years, is being launched to in part meet this need”.



# Marijuana and the developing brain

Structural and fMRI studies consistently find negative effect of cannabis on structure and functioning of:

Anterior cingulate

Cerebellum

Prefrontal cortex  
(specifically orbitofrontal cortex)

Necessary for long-term success into adulthood:

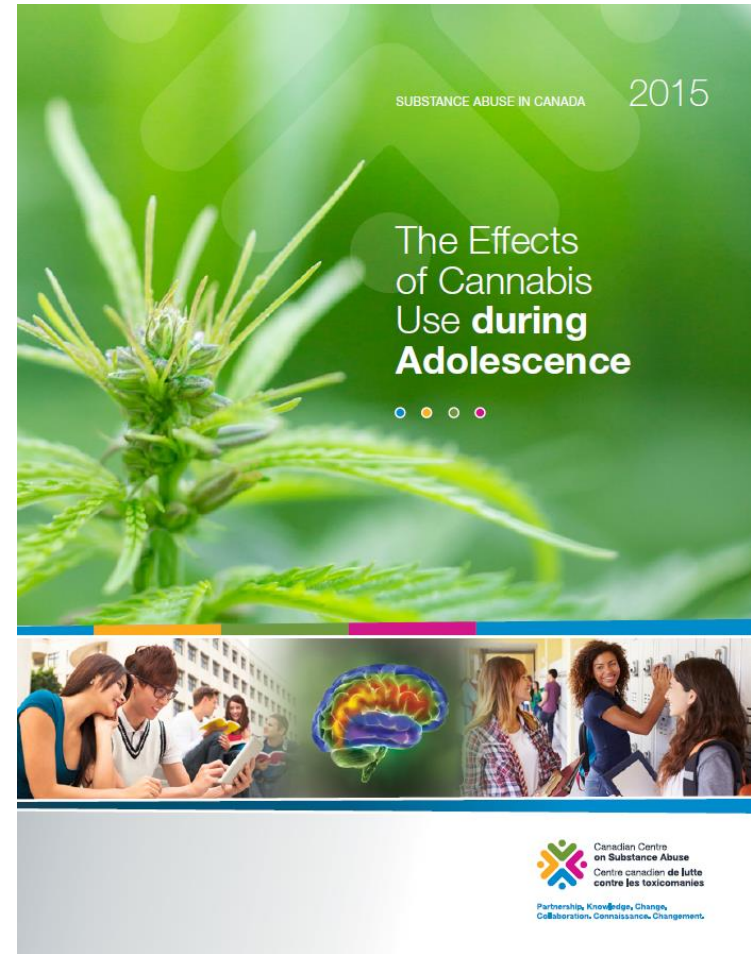
Executive  
functioning

Decision making

Response  
inhibition

Ability to carry  
out goal-directed  
behavior

Further research required





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# Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013

Deborah S. Hasin, PhD; Tulshi D. Saha, PhD; Bradley T. Kerridge, PhD; Risë B. Goldstein, PhD, MPH;  
S. Patricia Chou, PhD; Haitao Zhang, PhD; Jeeseun Jung, PhD; Roger P. Pickering, MS; W. June Ruan, MA;  
Sharon M. Smith, PhD; Boji Huang, MD, PhD; Bridget F. Grant, PhD, PhD

**IMPORTANCE** Laws and attitudes toward marijuana in the United States are becoming more permissive but little is known about whether the prevalence rates of marijuana use and marijuana use disorders have changed in the 21st century.

**OBJECTIVE** To present nationally representative information on the past-year prevalence rates of marijuana use, marijuana use disorder, and marijuana use disorder among marijuana users in the US adult general population and whether this has changed between 2001-2002 and 2012-2013.


**DESIGN, SETTING, AND PARTICIPANTS** Face-to-face interviews conducted in surveys of 2 nationally representative samples of US adults: the National Epidemiologic Survey on Alcohol and Related Conditions (data collected April 2001-April 2002; N = 43 093) and the National Epidemiologic Survey on Alcohol and Related Conditions-III (data collected April 2012-June 2013; N = 36 309). Data were analyzed March through May 2015.

**MAIN OUTCOMES AND MEASURES** Past-year marijuana use and *DSM-IV* marijuana use disorder (abuse or dependence).

**RESULTS** The past-year prevalence of marijuana use was 4.1% (SE, 0.15) in 2001-2002 and 9.5% (SE, 0.27) in 2012-2013, a significant increase ( $P < .05$ ). Significant increases were also found across demographic subgroups (sex, age, race/ethnicity, education, marital status, income, urban/rural, and region). The past-year prevalence of *DSM-IV* marijuana use disorder was 1.5% (0.08) in 2001-2002 and 2.9% (SE, 0.13) in 2012-2013 ( $P < .05$ ). With few exceptions, increases in the prevalence of marijuana use disorder between 2001-2002 and 2012-2013 were also statistically significant ( $P < .05$ ) across demographic subgroups. However, the prevalence of marijuana use disorder among marijuana users decreased significantly from 2001-2002 (35.6%; SE, 1.37) to 2012-2013 (30.6%; SE, 1.04).

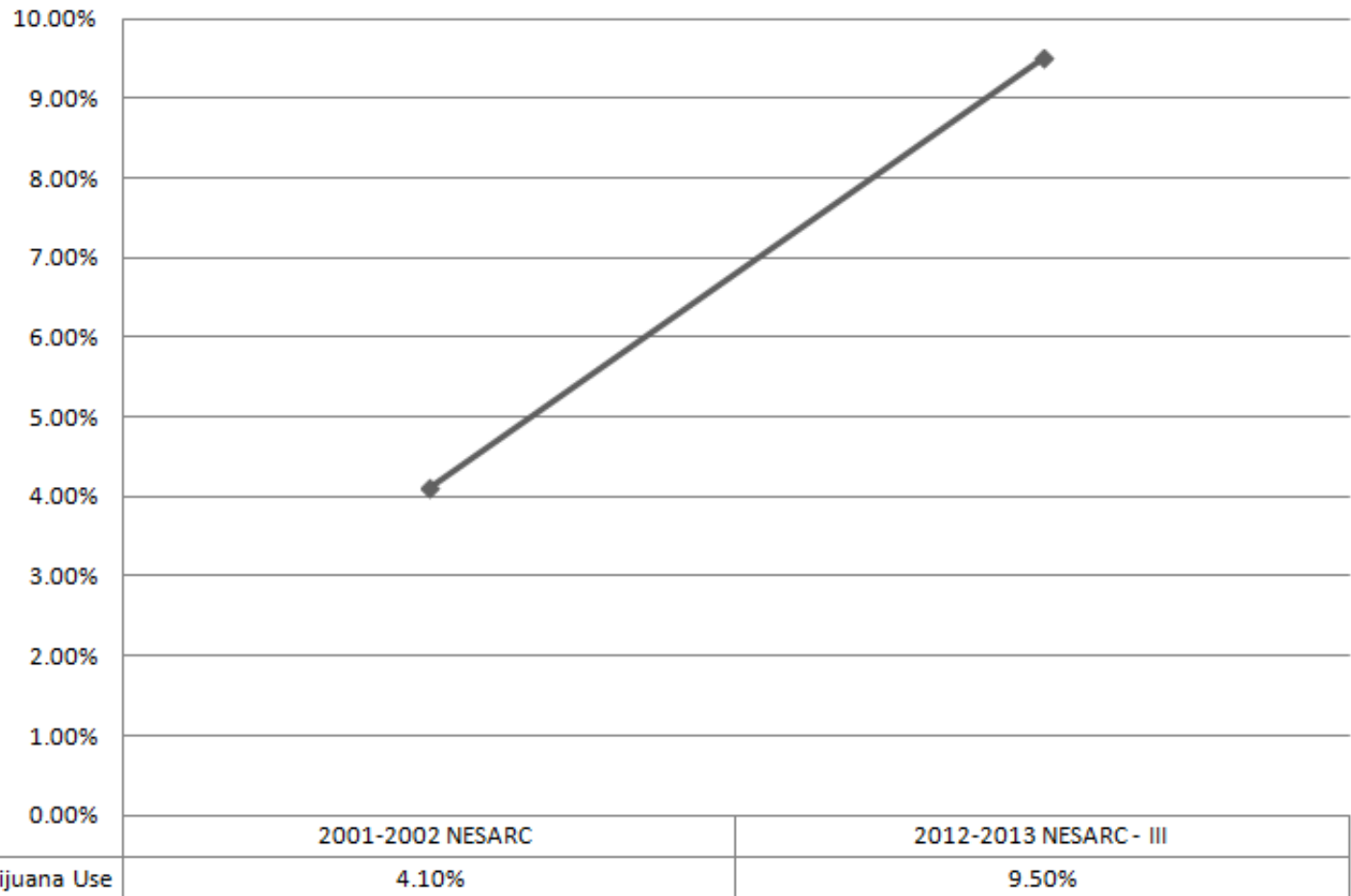
**CONCLUSIONS AND RELEVANCE** The prevalence of marijuana use more than doubled between 2001-2002 and 2012-2013, and there was a large increase in marijuana use disorders during that time. While not all marijuana users experience problems, nearly 3 of 10 marijuana users manifested a marijuana use disorder in 2012-2013. Because the risk for marijuana use disorder did not increase among users, the increase in prevalence of marijuana use disorder is owing to an increase in prevalence of users in the US adult population. Given changing laws and attitudes toward marijuana, a balanced presentation of the likelihood of adverse consequences of marijuana use to policy makers, professionals, and the public is needed.

# Data

- ▶ Compared the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) to the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions – III (NESARC III)
  - ▶ Weighted cross-tabulations estimated the prevalence of marijuana use and marijuana use disorder in the total samples and subsamples.
- 

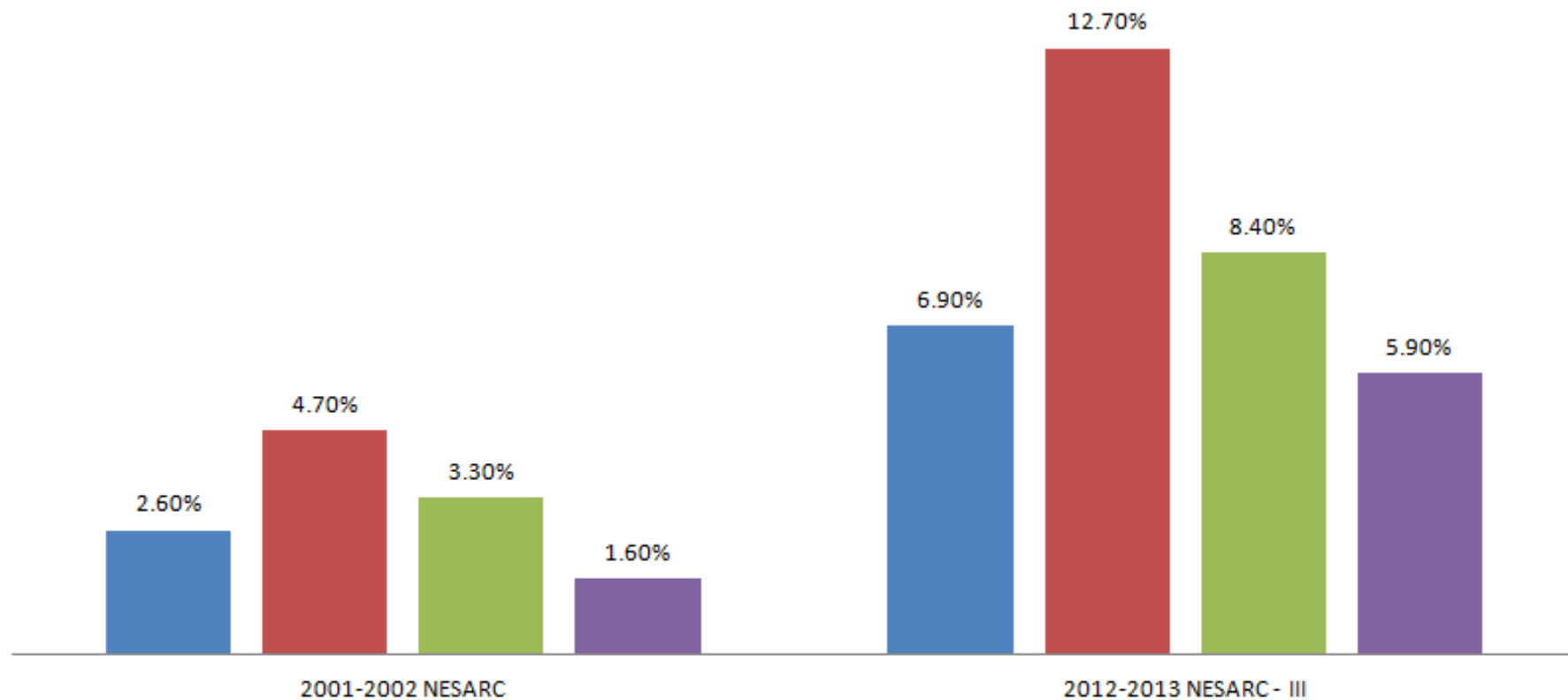
# Results: Change in Marijuana Use

**Overall Marijuana Use**



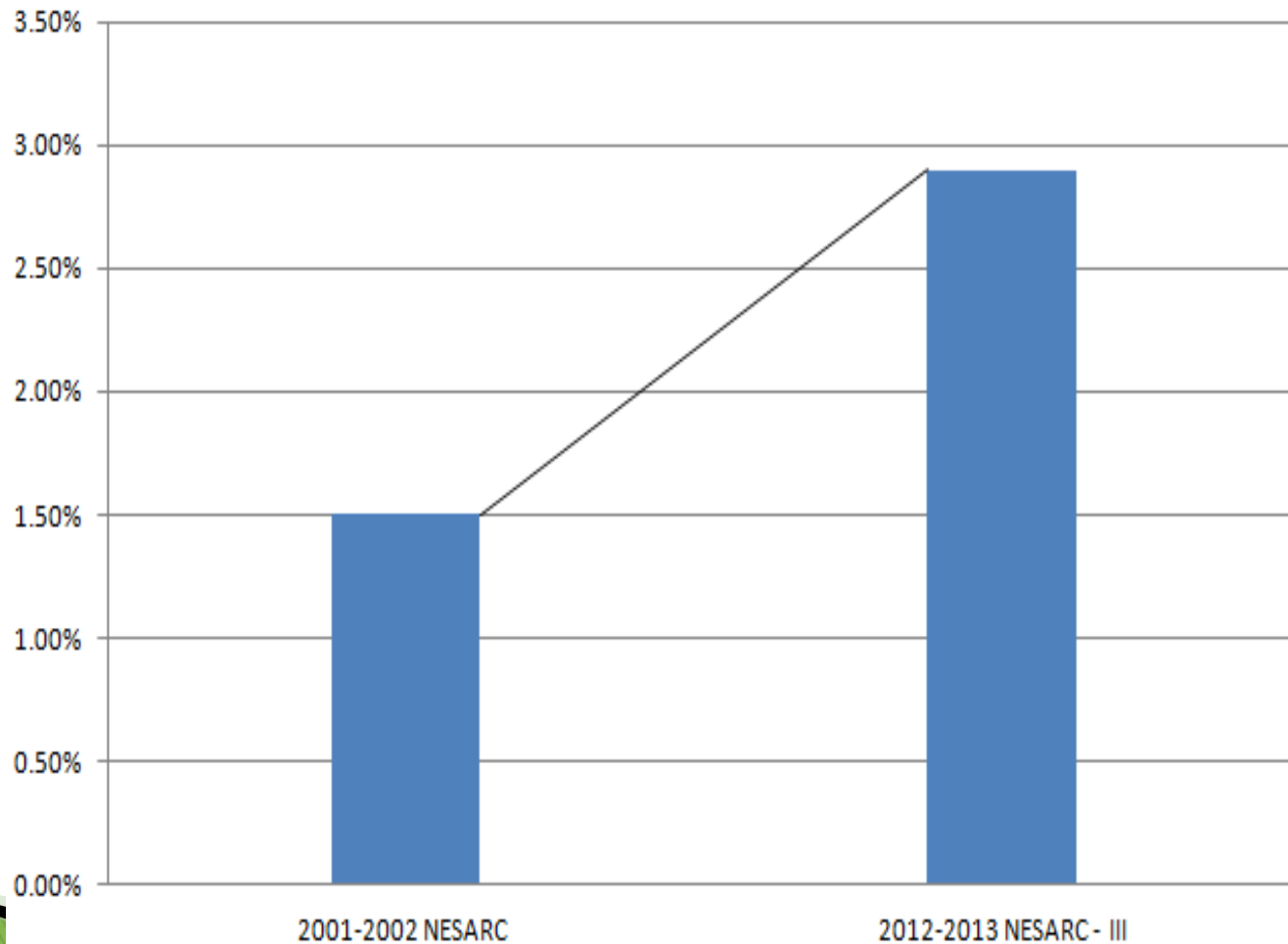
## Most Notable Increases Among Population Subgroups

■ Women ■ Black ■ Hispanic ■ Middle-Aged

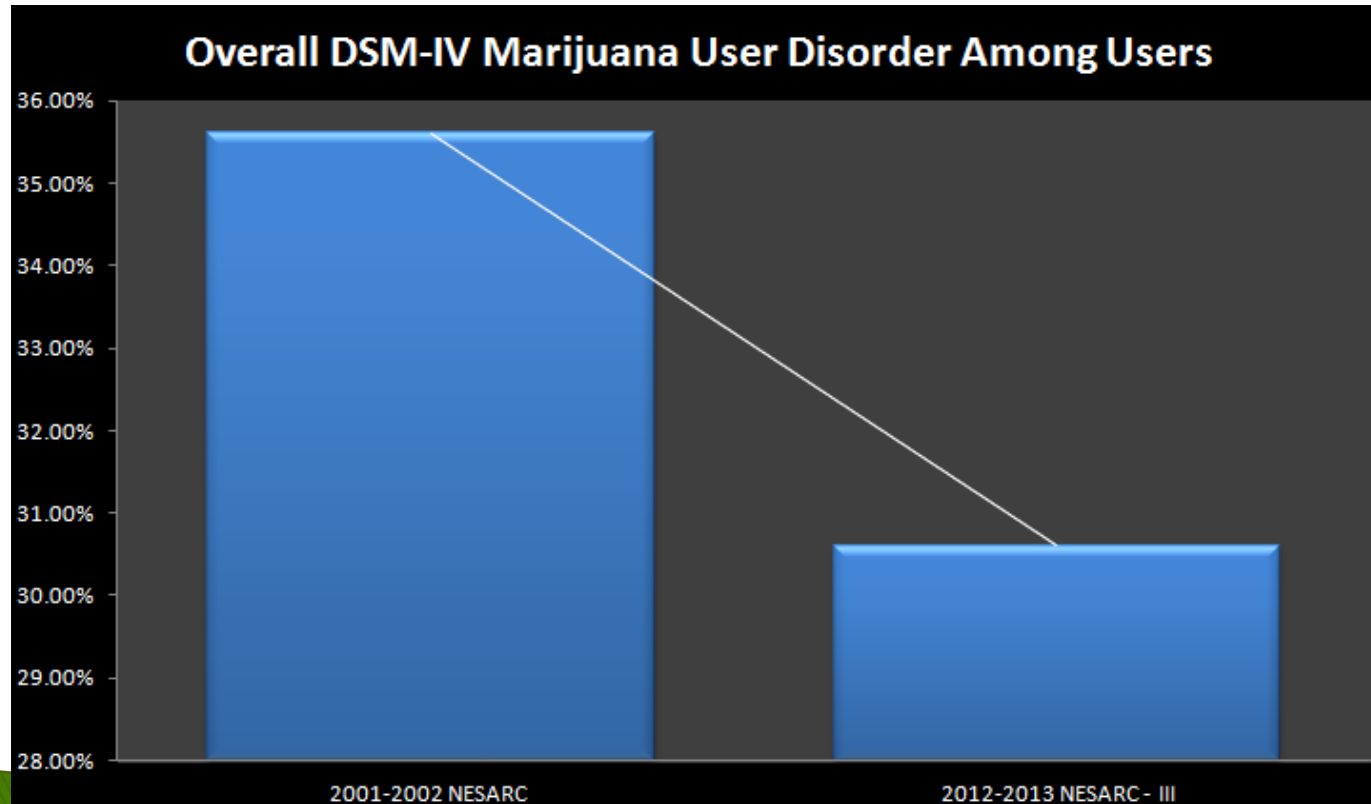


# Past Year *DSM-IV* Marijuana Use Disorder

## Overall DSM-IV Marijuana Use Disorder



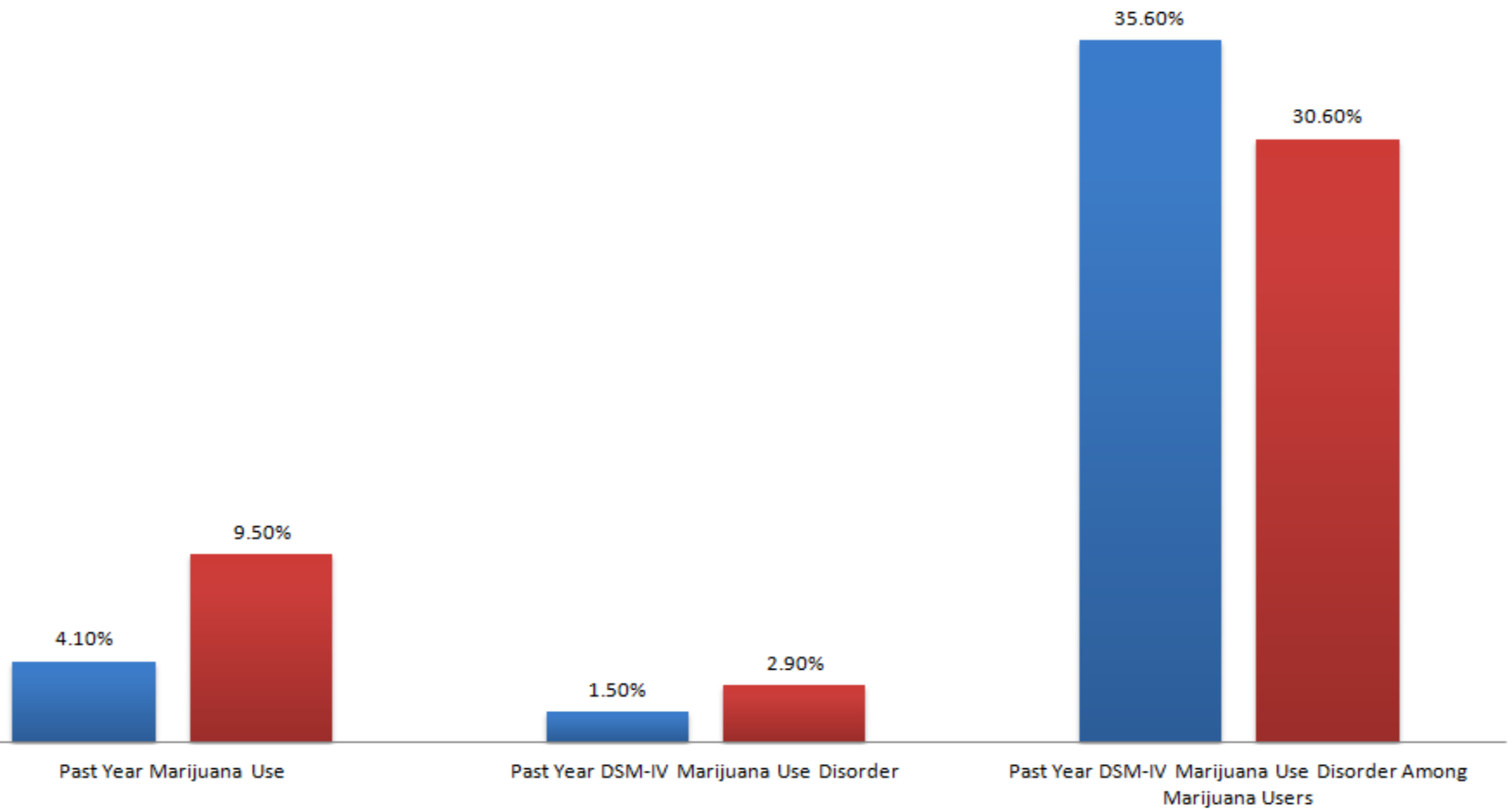
# Past Year DSM-IV Marijuana Use Disorders Among Marijuana Users



This indicated a significant decrease, particularly among men, those aged 18-29.

# Results

■ 2001-2002 NESARC ■ 2012-2013 NESARC - III



# Pediatric Marijuana Exposures in a Medical Marijuana State

George Sam Wang, MD; Genie Roosevelt, MD, MPH; Kennon Heard, MD

← Editorial pages 600 and 602

**IMPORTANCE** An increasing number of states are decriminalizing the use of medical marijuana, and the effect on the pediatric population has not been evaluated.

**OBJECTIVE** To compare the proportion of marijuana ingestions by young children who sought care at a children's hospital in Colorado before and after modification of drug enforcement laws in October 2009 regarding medical marijuana possession.

**DESIGN** Retrospective cohort study from January 1, 2005, through December 31, 2011.

**SETTING** Tertiary-care children's hospital emergency department in Colorado.

**PARTICIPANTS** A total of 1378 patients younger than 12 years evaluated for unintentional ingestions: 790 patients before September 30, 2009, and 588 patients after October 1, 2009.

**MAIN EXPOSURE** Marijuana ingestion.

**MAIN OUTCOMES AND MEASURES** Marijuana exposure visits, marijuana source, symptoms, and patient disposition.

**RESULTS** The proportion of ingestion visits in patients younger than 12 years (age range, 8 months to 12 years) that were related to marijuana exposure increased after September 30, 2009, from 0 of 790 (0%; 95% CI, 0%-0.6%) to 14 of 588 (2.4%; 95% CI, 1.4%-4.0%) ( $P < .001$ ). Nine patients had lethargy, 1 had ataxia, and 1 had respiratory insufficiency. Eight patients were admitted, 2 to the intensive care unit. Eight of the 14 cases involved medical marijuana, and 7 of these exposures were from food products.

**CONCLUSIONS AND RELEVANCE** We found a new appearance of unintentional marijuana ingestions by young children after modification of drug enforcement laws for marijuana possession in Colorado. The consequences of unintentional marijuana exposure in children should be part of the ongoing debate on legalizing marijuana.

*JAMA Pediatr.* 2013;167(7):630-633. doi:10.1001/jamapediatrics.2013.140  
Published online May 27, 2013.

**Author Affiliations:** Rocky Mountain Poison and Drug Center, Denver Health, Denver, Colorado (Wang, Heard); Department of Pediatrics, Section of Emergency Medicine, University of Colorado School of Medicine, Aurora (Roosevelt).

**Corresponding Author:** George Sam Wang, MD, Rocky Mountain Poison and Drug Center, 777 Bannock St, Office Box 0180, Denver, CO 80204 (george.wang@childrenscolorado.org).

# Data

- ▶ Participants from the state of Colorado (N=1378; age under 12) were evaluated for accidental ingestion from 1/1/2005 to 9/30/2009 (N=790) and from 10/1/2009 through 12/31/2011 (N=588)
- ▶ Significant increase in visits related to unintended ingestion among participants due to marijuana exposure after 9/2009 ( $p < 0.001$ )

**Table 1. Demographics of Patients Seen in the Children's Hospital Emergency Department for Ingestions<sup>a</sup>**

| Characteristic       | January 1, 2005,<br>Through September 30,<br>2009 | October 1, 2009,<br>Through December 31,<br>2011 |
|----------------------|---|--|
| No. of patients      | 790   | 588  |
| Age, median (IQR), y | 2.6 (1.6-3.0)                                     | 2.3 (1.5-3.6)                                    |
| Male sex             | 449 (56.8)  | 334 (56.8)                                       |
| Types of ingestions  |   |  |
| Acetaminophen        | 90 (11.3)   | 48 (8.2)   |
| Antihistamine        | 43 (5.4)  | 32 (5.4)   |
| Antidepressant       | 23 (2.9)  | 14 (2.3)   |
| Antitussive          | 18 (2.2)  | 14 (2.3)   |
| Marijuana exposures  | 0   | 14 (2.3)   |

Abbreviation: IQR, interquartile range.

<sup>a</sup> Values are given as number (percentage) unless otherwise noted.

# Monitoring Health Concerns Related to Marijuana in Colorado: 2014

Changes in Marijuana Use Patterns,  
Systematic Literature Review, and  
Possible Marijuana-Related Health Effects



**COLORADO**

Department of Public  
Health & Environment

**Figure 1. Rates of Hospitalizations (HD) and Emergency Department (ED) Visits with Possible Marijuana Exposures<sup>a</sup> in Children Up to 9 Years per 100,000 HD and ED Visits in Children Under 9 Years Old by Time Period in Colorado.**

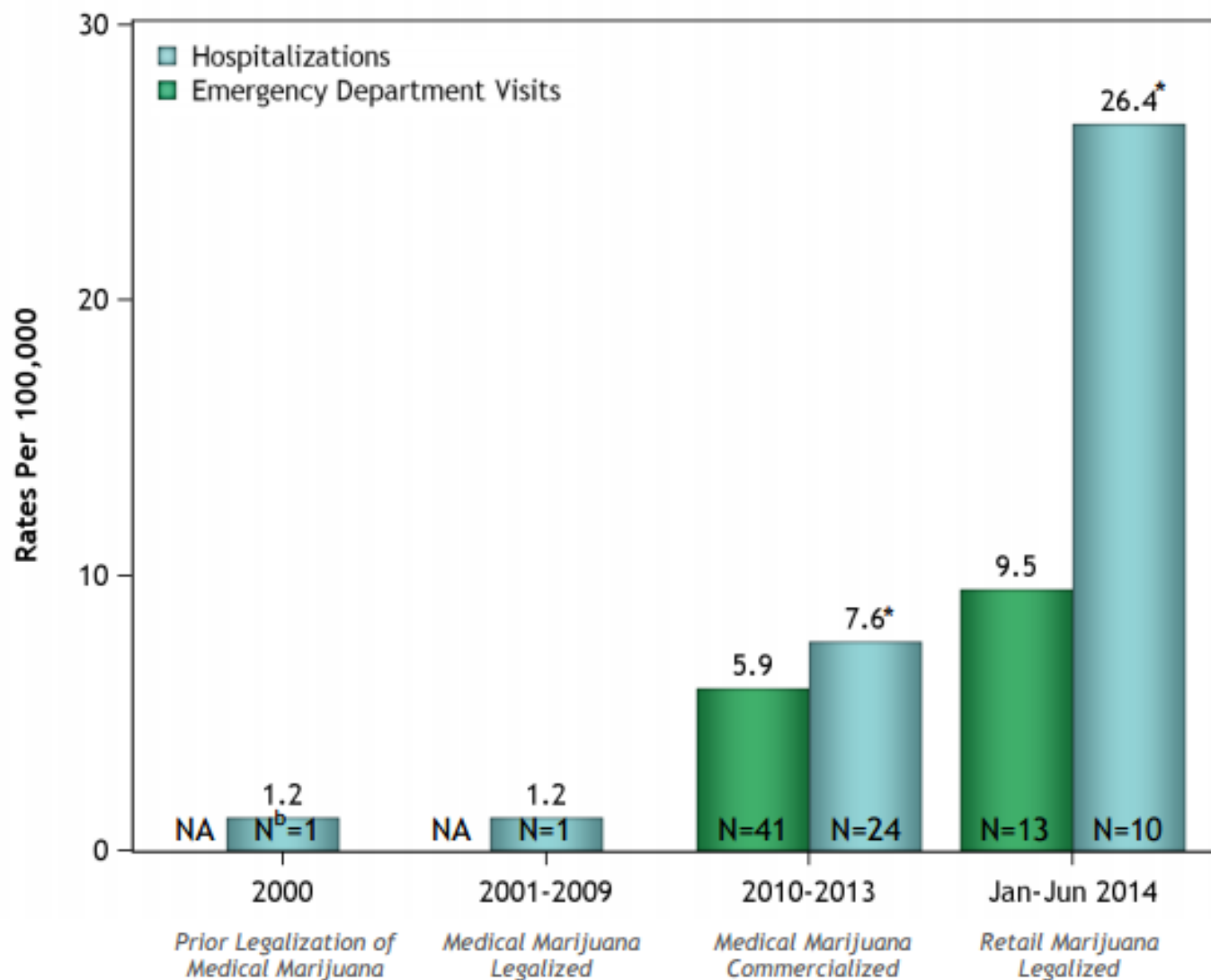
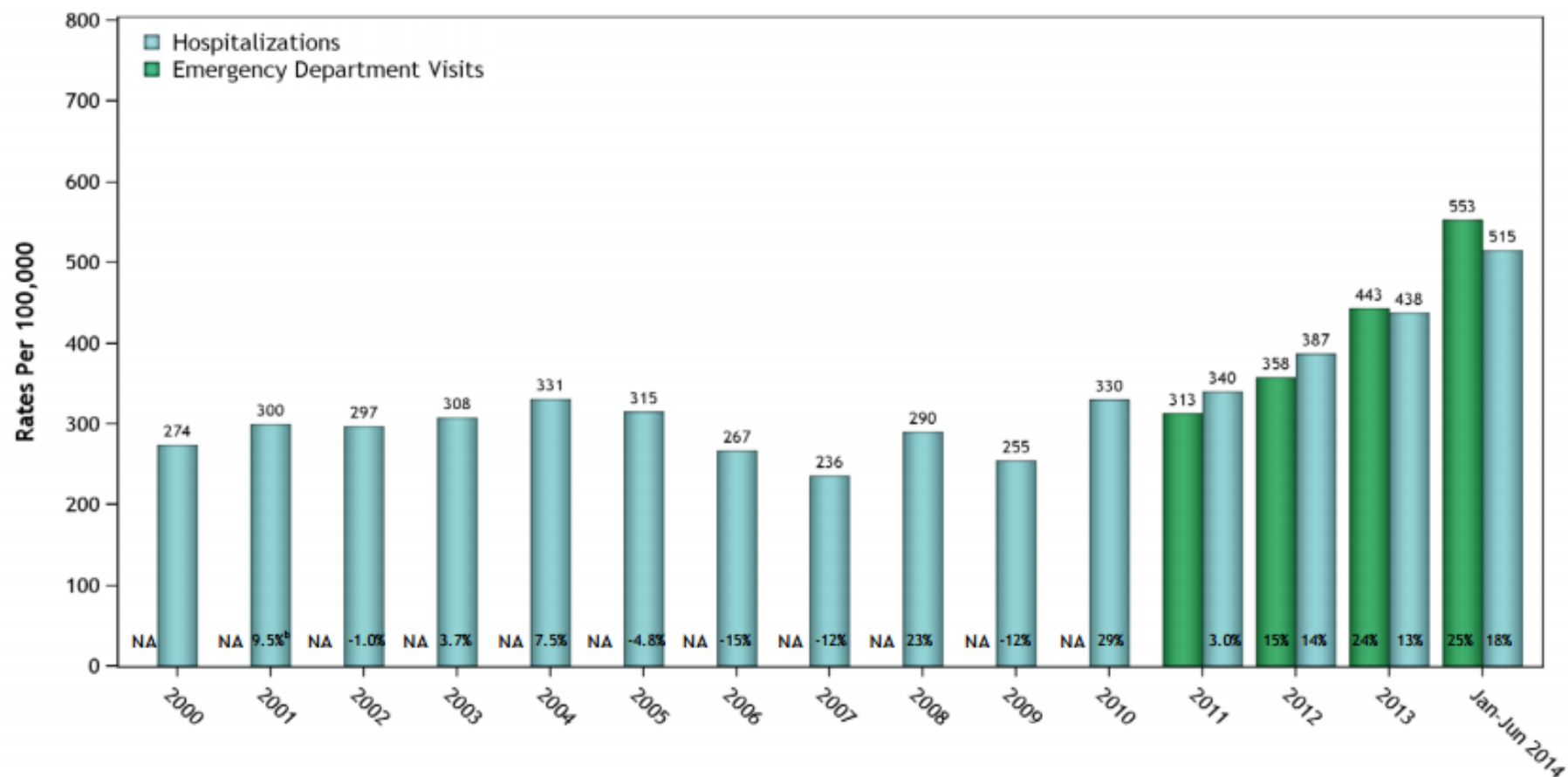


Figure 3. Rates of Hospitalizations (HD) and Emergency Department (ED) Visits with Possible Marijuana Exposures, Diagnoses, or Billing Codes<sup>a</sup> in the First Three Diagnosis Codes per 100,000 HD and ED Visits by Year in Colorado.



# Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado\*

Stacy Salomonsen-Sautel<sup>1</sup>, Sung-Joon Min<sup>1</sup>, Joseph T. Sakai<sup>1</sup>, Christian Thurstone<sup>1,2</sup>, and Christian Hopfer<sup>1</sup>

<sup>1</sup>Department of Psychiatry, University of Colorado Anschutz Medical Campus, Aurora, CO, 80045

<sup>2</sup>Denver Health and Hospital Authority, Denver, CO, 80204

## Abstract

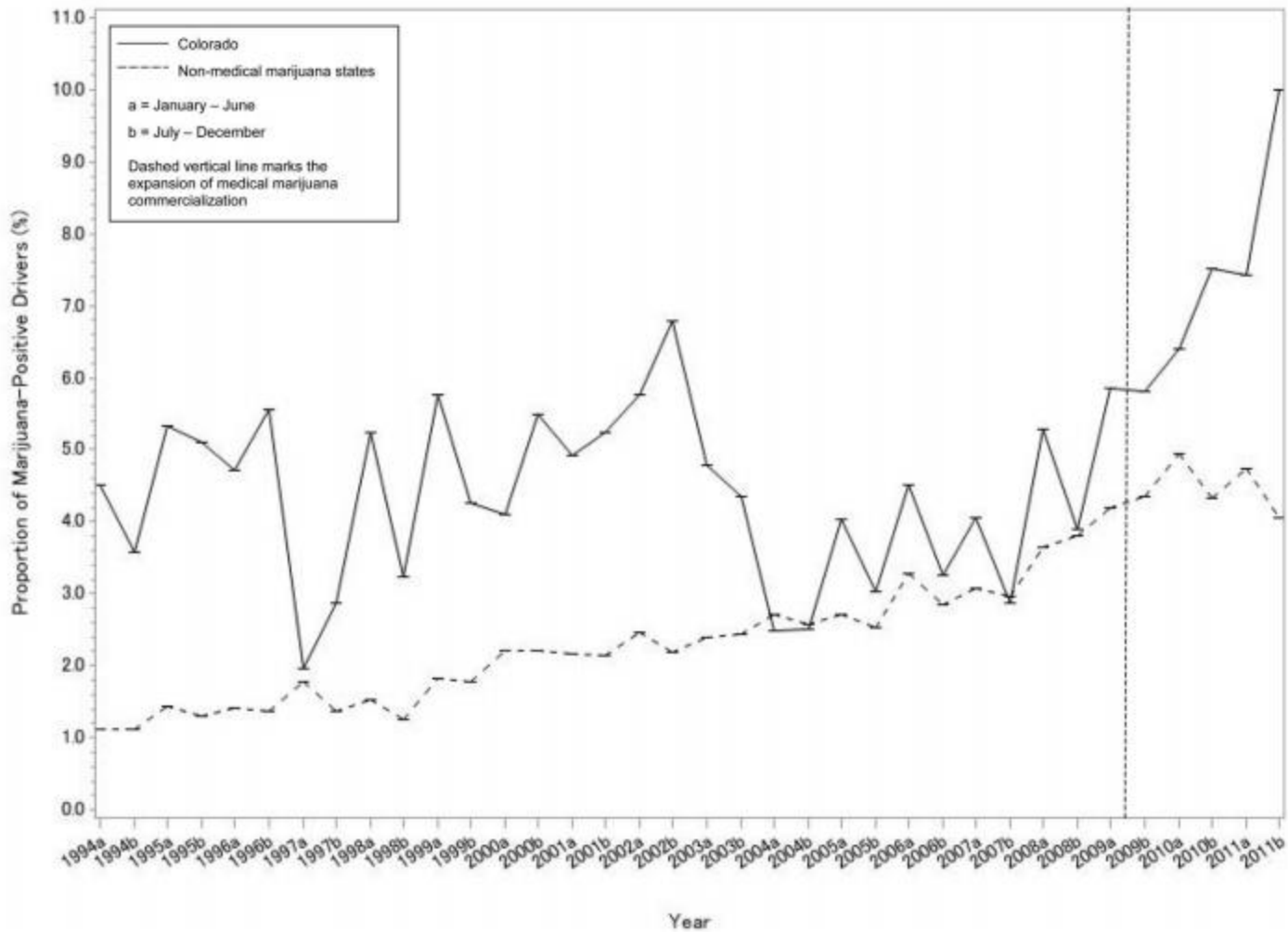
**Background**—Legal medical marijuana has been commercially available on a widespread basis in Colorado since mid-2009; however, there is a dearth of information about the impact of marijuana commercialization on impaired driving. This study examined if the proportions of drivers in a fatal motor vehicle crash who were marijuana-positive and alcohol-impaired, respectively, have changed in Colorado before and after mid-2009 and then compared changes in Colorado with 34 non-medical marijuana states (NMMS).

**Methods**—Thirty-six 6-month intervals (1994–2011) from the Fatality Analysis Reporting System were used to examine temporal changes in the proportions of drivers in a fatal motor vehicle crash who were alcohol-impaired ( $\geq 0.08$  g/dl) and marijuana-positive, respectively. The pre-commercial marijuana time period in Colorado was defined as 1994–June 2009 while July 2009–2011 represented the post-commercialization period.

**Results**—In Colorado, since mid-2009 when medical marijuana became commercially available and prevalent, the trend became positive in the proportion of drivers in a fatal motor vehicle crash who were marijuana-positive (change in trend, 2.16 (0.45),  $p < 0.0001$ ); in contrast, no significant changes were seen in NMMS. For both Colorado and NMMS, no significant changes were seen in the proportion of drivers in a fatal motor vehicle crash who were alcohol-impaired.

# Data

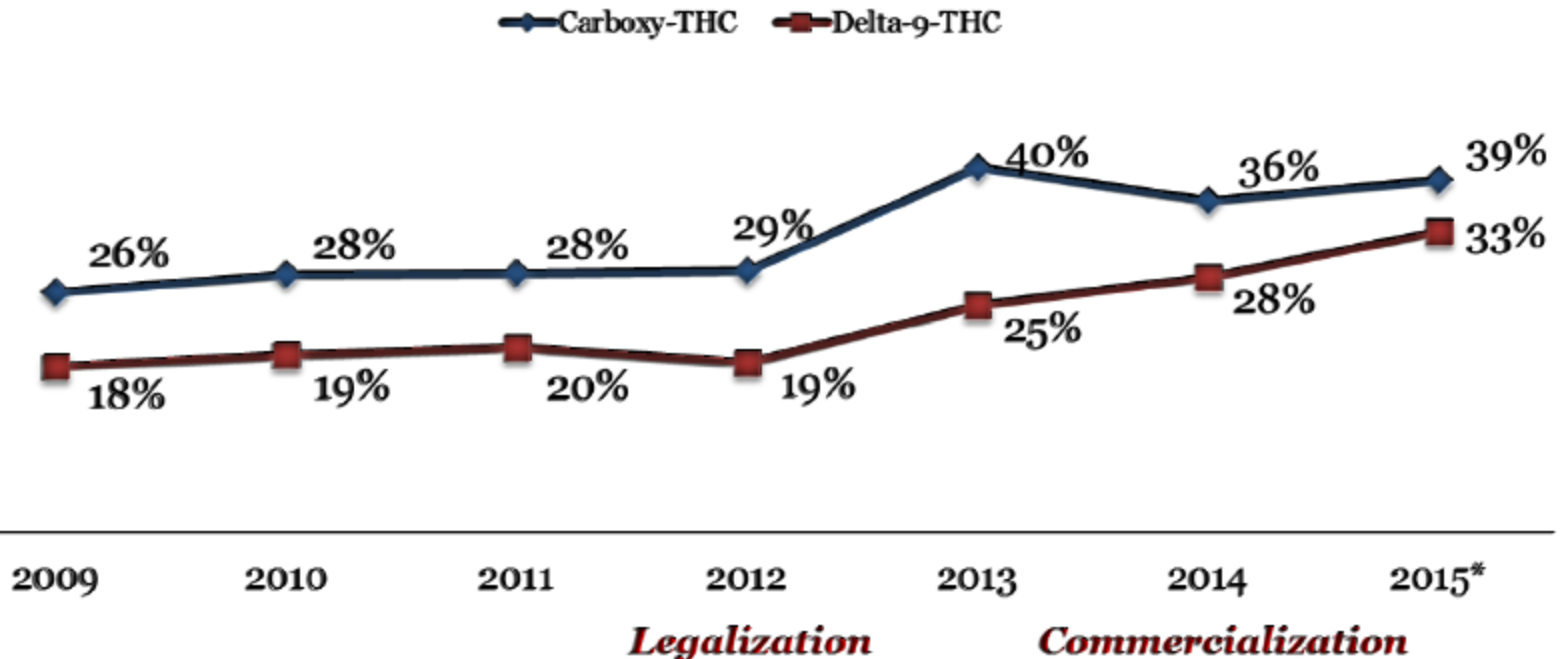
- ▶ Data from the Fatality Analysis Reporting System (FARS) was analyzed from 1994–2011 in six month intervals to examine the trends of individuals in a fatal car crash before and after legalization of marijuana in Colorado.
- ▶ Results indicated that since legalization, there has been a positive trend in the proportion of individuals involved in a fatal car crash who were marijuana-positive ( $p < 0.0001$ )



**Figure 2.**  
Proportion of drivers in a fatal motor vehicle crash who were marijuana-positive in Colorado and 34 states without medical marijuana laws from 1994–2011

# Washington State Report

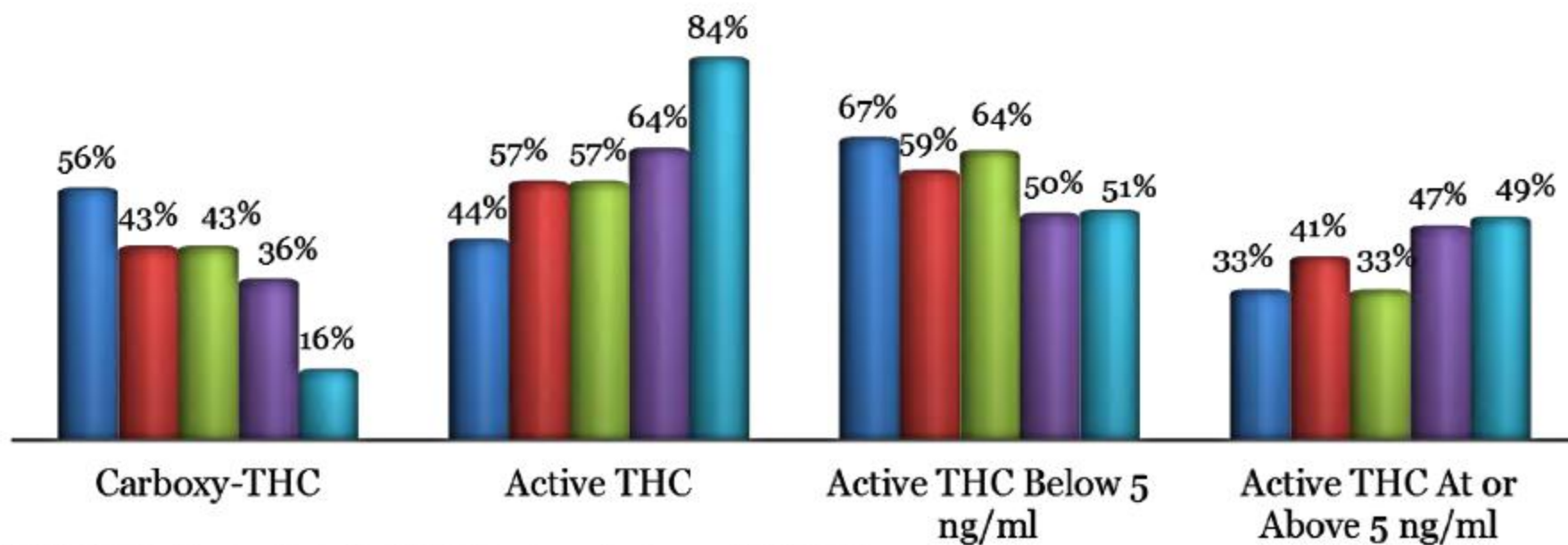
**Percentage of Total Driving Cases Positive for Carboxy-THC and Delta-9-THC 2009-2015\***



SOURCE: Washington State Patrol Toxicology Laboratory and NWHIDTA  
2015\*: January through April 2015

## Drivers Positive for Any Cannabinoid

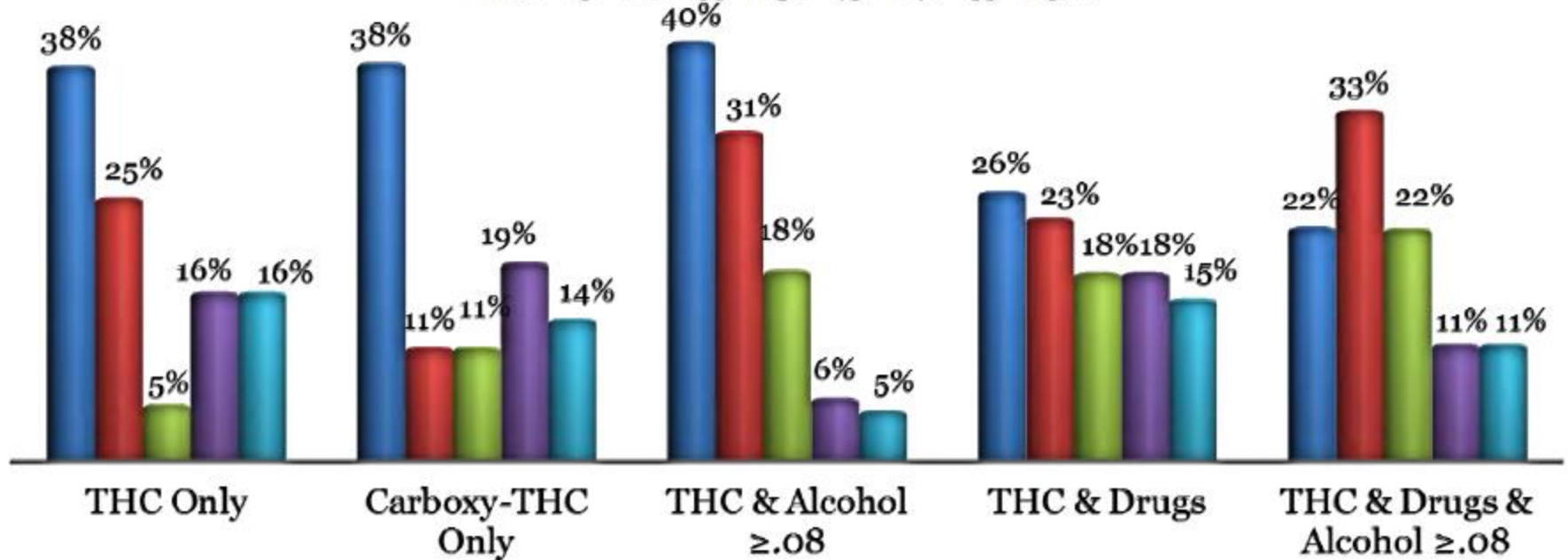
■ 2010 ■ 2011 ■ 2012 ■ 2013 ■ 2014



SOURCE: Washington State Traffic Safety Commission and NWHIDTA

## Drivers by Age

■ 16 - 25 ■ 26 - 35 ■ 36 - 45 ■ 46 - 55 ■ 56+



SOURCE: Washington State Traffic Safety Commission and NWHIDTA

# Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier<sup>a,b,1</sup>, Avshalom Caspi<sup>a,b,c,d,e</sup>, Antony Ambler<sup>e,f</sup>, HonaLee Harrington<sup>b,c,d</sup>, Renate Houts<sup>b,c,d</sup>, Richard S. E. Keefe<sup>d</sup>, Kay McDonald<sup>f</sup>, Aimee Ward<sup>f</sup>, Richie Poulton<sup>f</sup>, and Terrie E. Moffitt<sup>a,b,c,d,e</sup>

<sup>a</sup>Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, <sup>b</sup>Department of Psychology and Neuroscience, and <sup>c</sup>Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; <sup>d</sup>Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; <sup>e</sup>Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and <sup>f</sup>Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

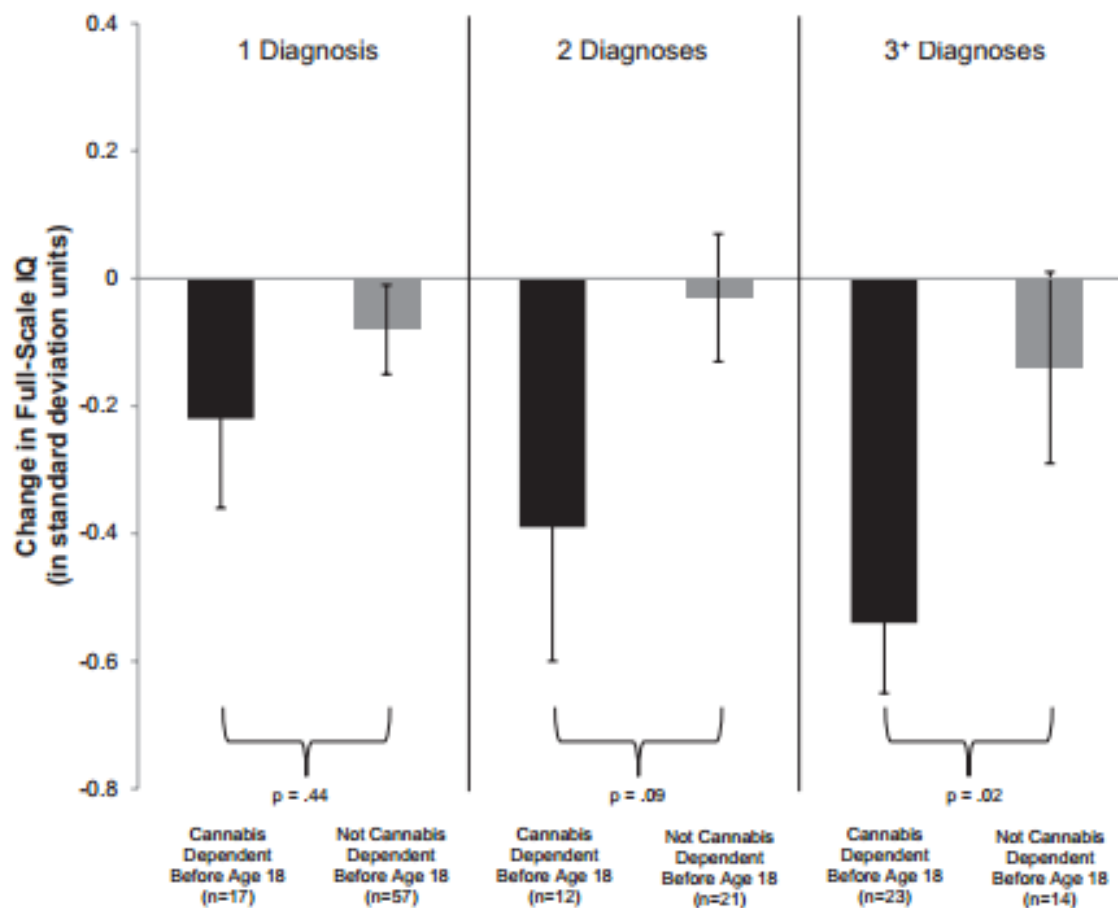
Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y. Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents.

nence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is reliance on retrospectively reported quantity, frequency, duration, and age-of-onset of cannabis use, often inquired about years after initiation of heavy use.

A prospective, longitudinal investigation of the association between cannabis use and neuropsychological impairment could redress these limitations and strengthen the existing evidence base by assessing neuropsychological functioning in a sample of youngsters before the onset of cannabis use, obtaining prospective data on cannabis use as the sample is followed over a number of years, and readministering neuropsychological tests after some members of the sample have developed a pattern of long-term cannabis use. To our knowledge, only one prospective, longitudinal study of the effects of cannabis on neuropsychological functioning has been conducted (21), and, in this study, the sample was small and the average duration of regular cannabis use was only 2 y.

In the present study, we investigated the association between persistent cannabis use—prospectively assessed over 20 y—and



**Fig. 2.** Adolescent vulnerability. Shown is change in full-scale IQ (in SD units) from childhood to adulthood among study members with 1, 2, or 3+ diagnoses of cannabis dependence as a function of age of onset of cannabis dependence. Individuals with adolescent-onset cannabis dependence (black bars) experienced greater IQ decline than individuals with adult-onset cannabis dependence (gray bars). IQ decline of approximately  $-0.55$  SD units among individuals with adolescent-onset cannabis dependence in the 3+ group represents a decline of 8 IQ points. Error bars = SEs.

# MARIJUANA LEGALIZATION? POTENTIAL PUBLIC HEALTH AND SAFETY IMPACTS



JOHN F. KELLY, PhD

MARCH 30, 2016



MASSACHUSETTS  
GENERAL HOSPITAL



RECOVERY  
RESEARCH  
INSTITUTE



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MEDICAL SCHOOL

# THE DRUG PROBLEM ...

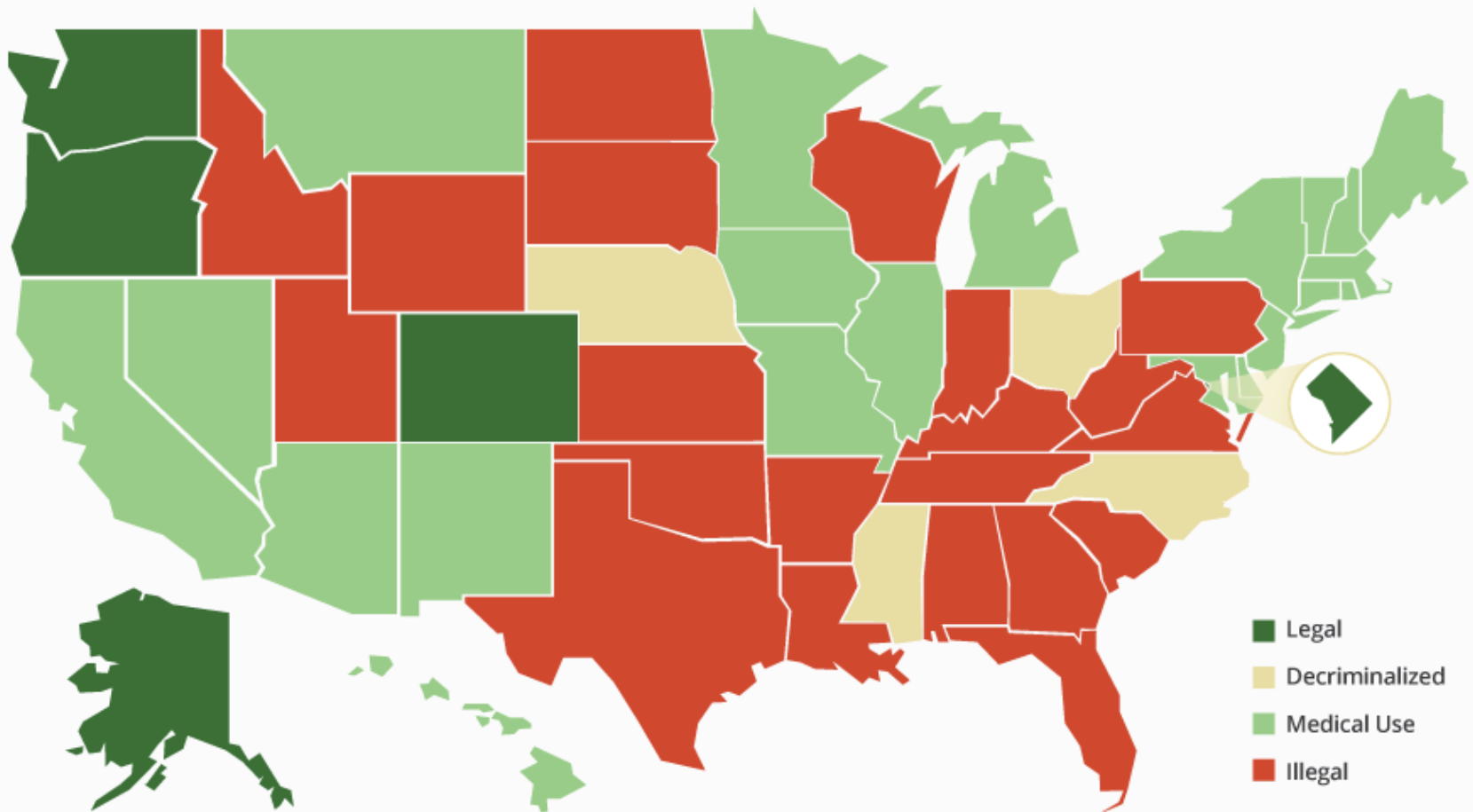
“FOR EVERY COMPLEX PROBLEM  
THERE IS A SOLUTION THAT IS CLEAR,  
SIMPLE, AND WRONG”

—HENRY L. MENCKEN

# LEGALIZATION? HOW DID WE GET HERE?



## Legality of Marijuana in the United States



Source: <http://www.economist.com/blogs/graphicdetail/2015/01/daily-chart-11>

DrugTreatment.com

“MEDICAL MARIJUANA”...



# FOR WHICH CONDITIONS MIGHT MARIJUANA/THC HAVE A THERAPEUTIC BENEFIT?

Up to 259 conditions including:

- ALZHEIMER'S DISEASE
- ANOREXIA
- HIV/AIDS
- ARTHRITIS
- CACHEXIA
- CANCER
- CROHN'S DISEASE
- EPILEPSY
- GLAUCOMA
- MIGRAINES
- MULTIPLE SCLEROSIS
- NAUSEA
- PAIN
- SPASTICITY
- WASTING SYNDROME

# CANNABIDOIDS HAVE DOCUMENTED THERAPEUTIC POTENTIAL...

## THC ADMINISTRATION & FDA APPROVED THC-BASED MEDICATIONS

| Compound             | Administration   | FDA Status   | Approved Locations                   | Purposes  |
|----------------------|------------------|--|--------------------------------------|---|
| Dronabinol (Marinol) | Oral capsule     | FDA-approved (1985)                                | USA, Germany                         | Nausea & vomiting related to cancer chemotherapy and wasting associated with AIDS |
| Nabilone (Cesamet)   | Oral capsule     | FDA-approved (1985)<br>*Marketed in the US in 2006 | USA, Canada, UK, Mexico              | Nausea & vomiting related to cancer chemotherapy                                  |
| Nabiximols (Sativex) | Oromucosal spray | Almost FDA-approved; late-stage clinical trials    | Canada, UK, other European countries | Multiple sclerosis spasticity, cancer pain, neuropathic pain                      |

"Marijuana Site Reclamation and Restoration Cost Analysis." U.S. Department of Interior, National Park Service. December 9, 2010 (unpublished data). <http://www.whitehouse.gov/ondcp/frequently-asked-questions-and-facts->



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Journal of  
ETHNO-  
PHARMACOLOGY

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## Review

# Cannabinoids in medicine: A review of their therapeutic potential

Mohamed Ben Amar

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Received 12 October 2005; received in revised form 30 January 2006; accepted 2 February 2006

## Abstract

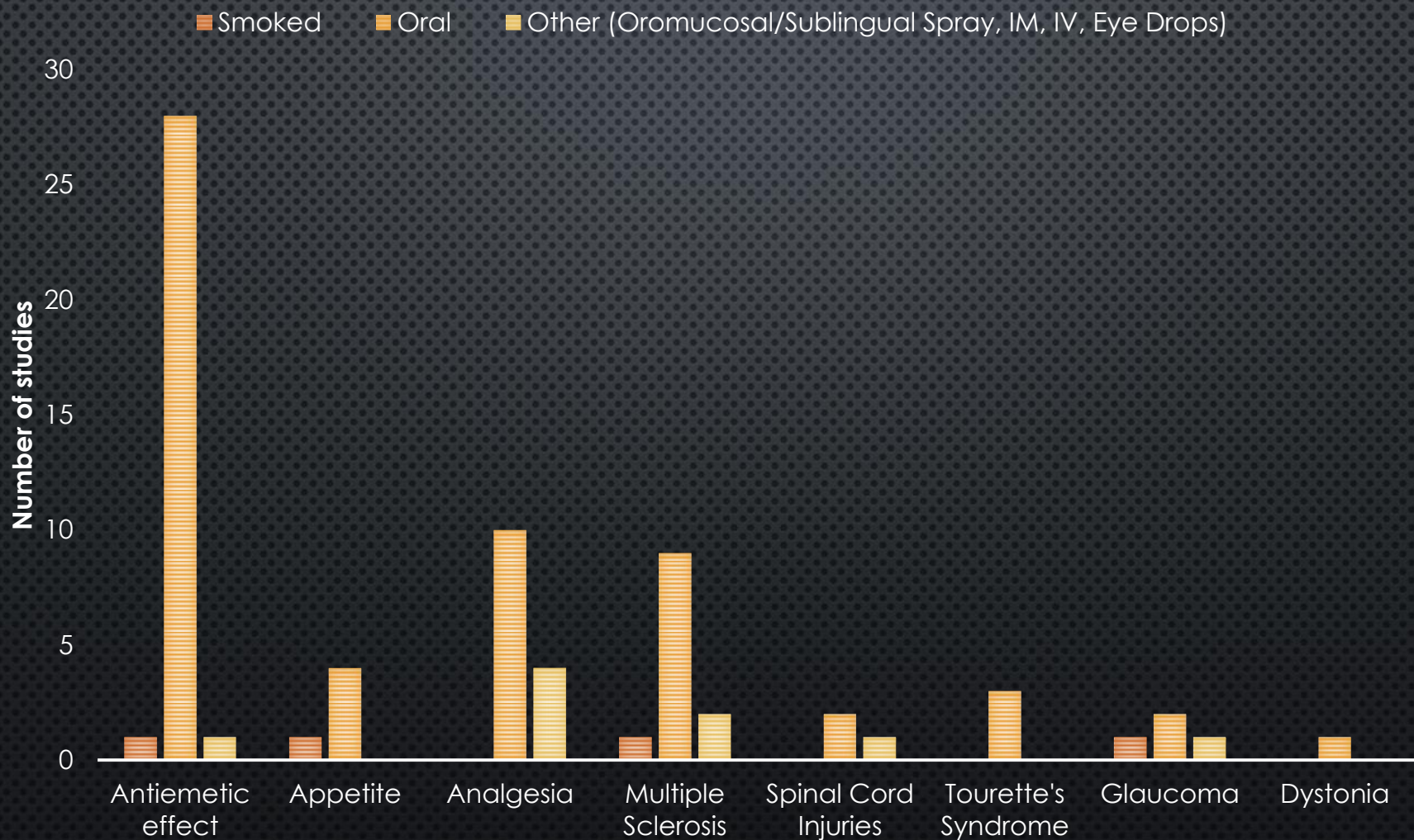
In order to assess the current knowledge on the therapeutic potential of cannabinoids, a meta-analysis was performed through Medline and PubMed up to July 1, 2005. The key words used were cannabis, marijuana, marihuana, hashish, hashich, haschich, cannabinoids, tetrahydrocannabinol, THC, dronabinol, nabilone, levonantradol, randomised, randomized, double-blind, simple blind, placebo-controlled, and human. The research also included the reports and reviews published in English, French and Spanish. For the final selection, only properly controlled clinical trials were retained, thus open-label studies were excluded.

Seventy-two controlled studies evaluating the therapeutic effects of cannabinoids were identified. For each clinical trial, the country where the project was held, the number of patients assessed, the type of study and comparisons done, the products and the dosages used, their efficacy and their adverse effects are described. Cannabinoids present an interesting therapeutic potential as antiemetics, appetite stimulants in debilitating diseases (cancer and AIDS), analgesics, and in the treatment of multiple sclerosis, spinal cord injuries, Tourette's syndrome, epilepsy and glaucoma.

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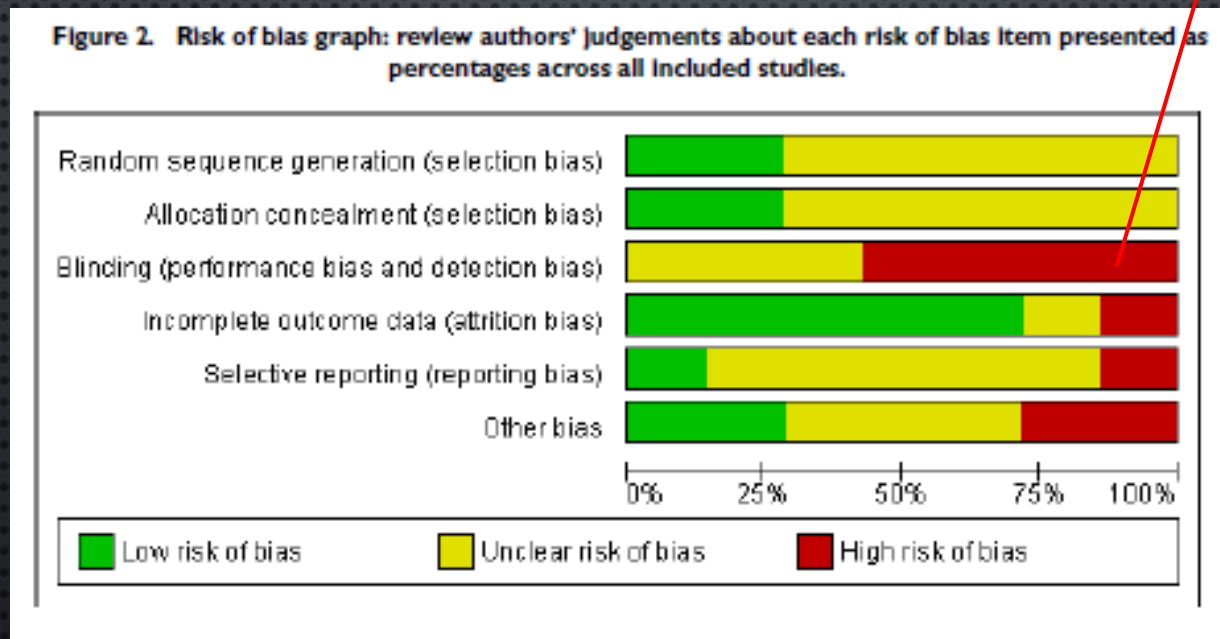
**Keywords:** Cannabinoids; Cannabis; Therapeutic potential; Controlled clinical trials; Efficacy; Safety

# CONTROLLED STUDIES EVALUATING THE THERAPEUTIC EFFECT OF THC BY ADMINISTRATION TYPE



Ben Amar, M. (2006). Cannabinoids in medicine: A review of their therapeutic potential. *Journal of ethnopharmacology*, 105(1), 1-25.

# ISSUES WITH BLINDING IN MEDICAL MARIJUANA RCTS



More than 50% of studies are considered at high risk for unblinding

The use of cannabis and rapidly acting cannabinoids pose considerable challenges for blinding, as the psychoactive effects are expected to be quickly discernible to study participants, particularly those who have been previous users of such products.

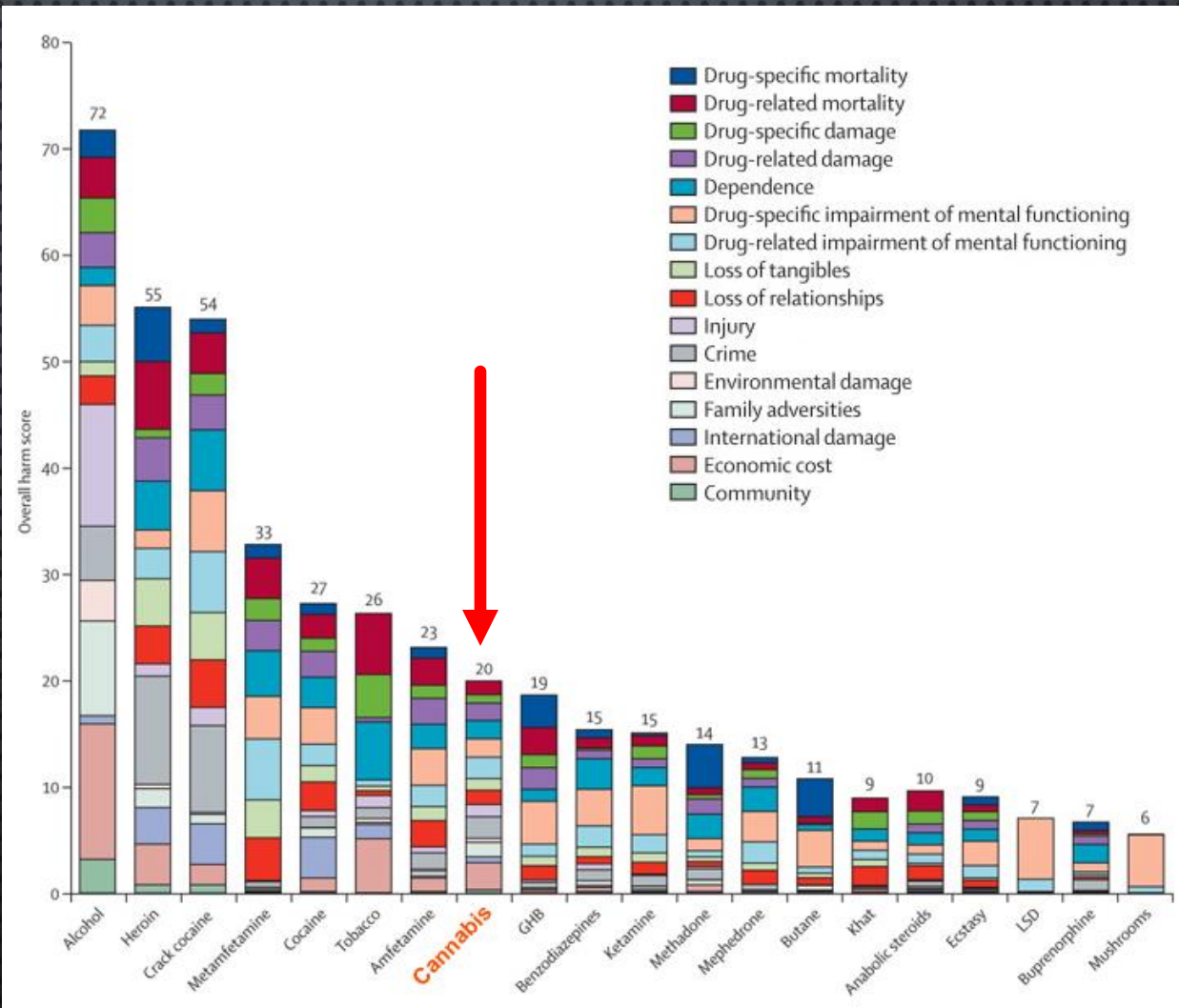
Lutge, E. E., Gray, A., & Siegfried, N. (2013). The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *status and date: New, published in*, (4).

WHY SHOULD MJ BE ILLEGAL?

WHY SHOULD IT BE LEGALIZED?

# HEALTH (AND SOCIETAL) RISKS OF SMOKED MARIJUANA

20 DRUGS RANKED BY  
OVERALL HARM  
ALONG 16 CRITERIA



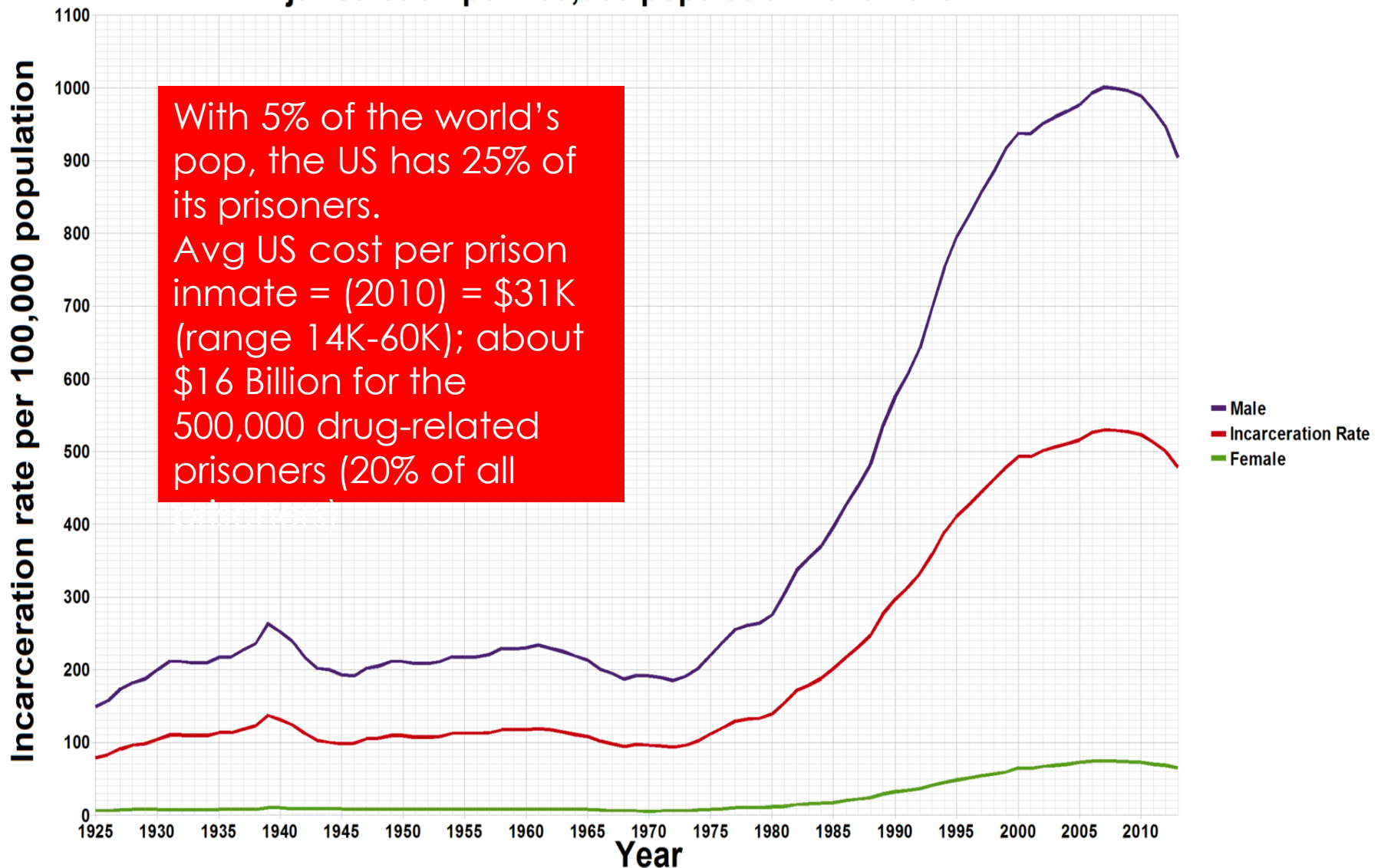
Nutt, D. J., King, L. A., & Phillips, L. D. (2010). Drug harms in the UK: a multicriteria decision analysis. *The Lancet*, 376(9752), 1558-1565.

# ARGUMENTS FOR CANNABIS LEGALIZATION

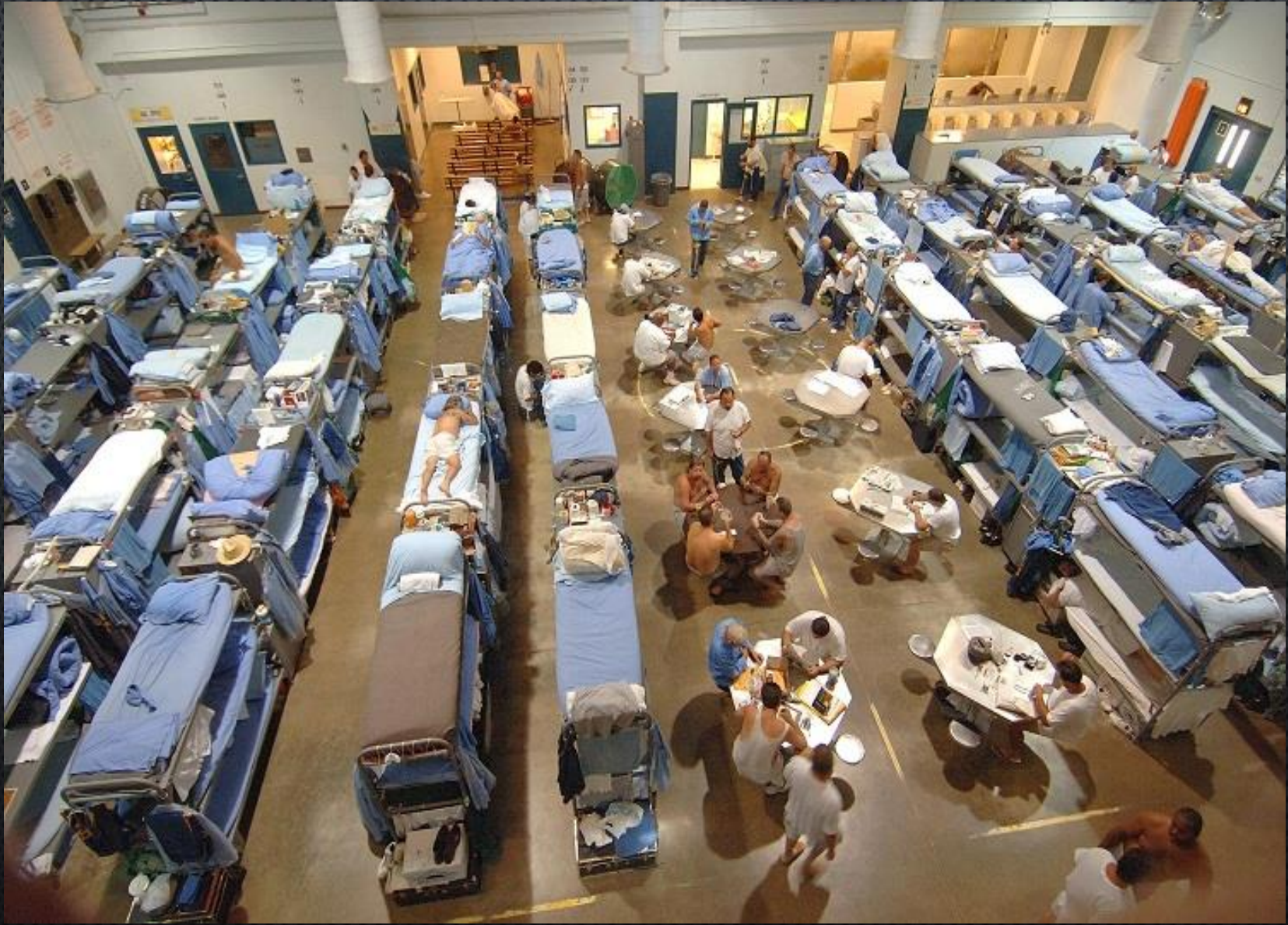
- “WAR ON DRUGS” HAS FAILED
- 5% OF WORLD’S POPULATION -25% OF WORLD’S PRISONERS
- 2.5 MILLION LOCKED UP; ABOUT 500,000 OF WHOM ARE THERE FOR DRUGS
- RACIAL DISPARITIES IN INCARCERATION RATES AT SAME PREVALENCE OF USE
- LEGALIZATION WOULD REDUCE ARRESTS/CRIMINAL JUSTICE COSTS (2013- 41% OF ALL ILLICIT DRUG-RELATED VIOLATIONS WERE MJ POSSESSION; 6% FOR MJ SALE/MANUFACTURING
- DEMAND IS HIGH- “GONNA DO IT ANYWAY” SO WHY NOT REGULATE IT AND MAKE IT SAFE?
- IT’S NOT BAD/AS BAD AS ALCOHOL/TOBACCO -EVEN GOOD FOR YOU (MEDICINAL)
- TAX IT AND BRING IN REVENUE FOR STATES

# The War on Drugs

**Incarceration rate of inmates incarcerated under state and federal jurisdiction per 100,000 population 1925-2013**

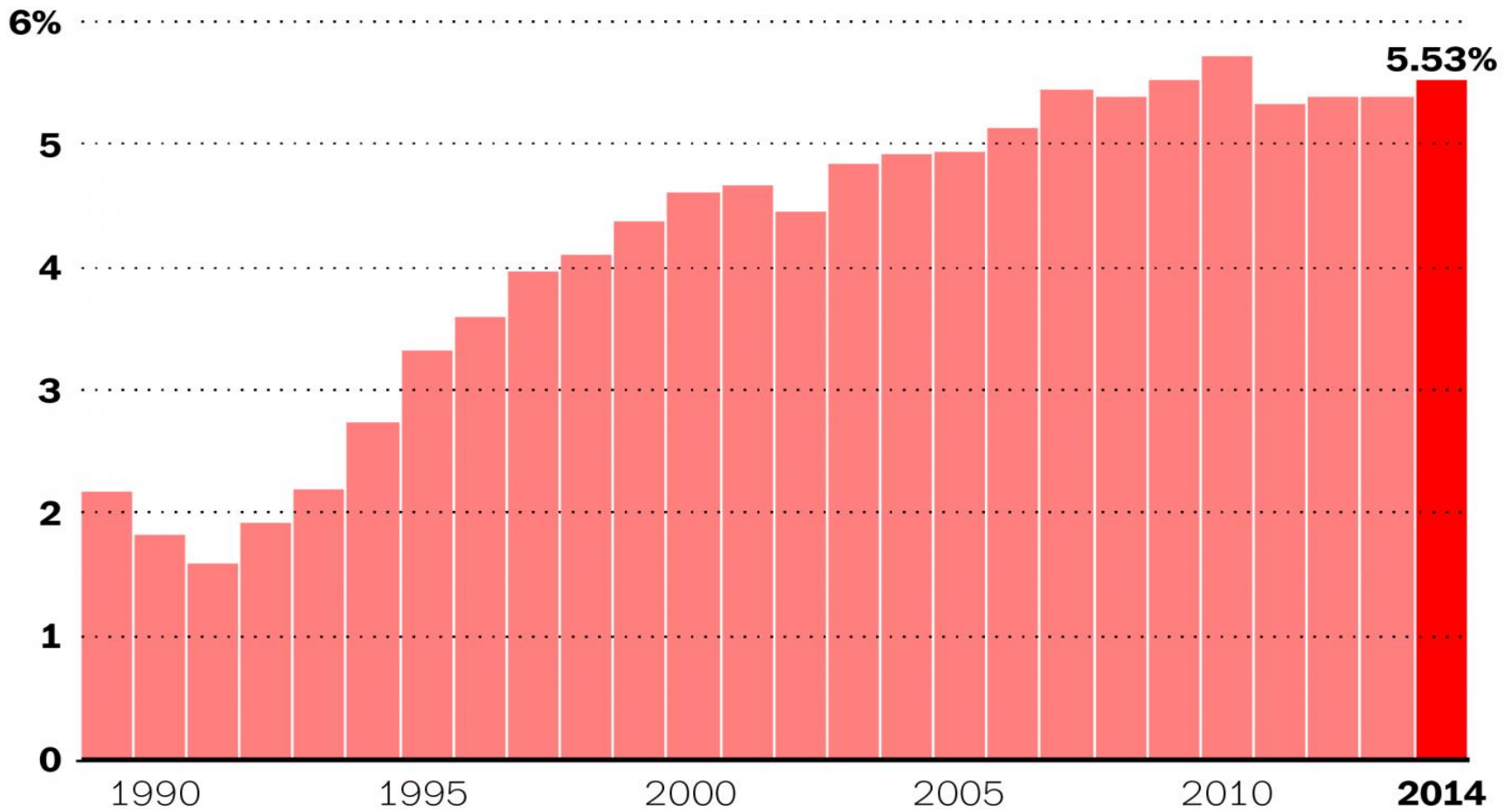


PRISONS OVERCROWDING: 20% (500,000) OF US PRISONERS ARE IN PRISON DUE TO DRUG OFFENCES; THE MAJORITY OF INMATES MEET CRITERIA FOR SUBSTANCE USE DISORDER/PSYCH ILLNESS



# As a share of all arrests, marijuana arrests remain near record highs

Marijuana possession arrests as a share of all arrests, 1989-2014



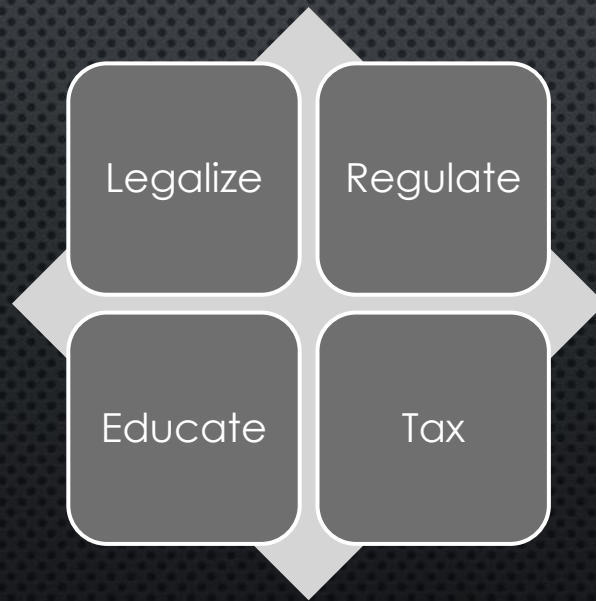
# SO, LEGALIZE?

- OF THE 2.5 MILLION PRISONERS IN US ABOUT 500,000 ARE THERE DUE TO DRUG LAW VIOLATIONS, **BUT ONLY ABOUT 40,000 OF THESE ARE MJ**
- THIS WOULD BE JUSTIFICATION FOR DECRIMINALIZATION NOT LEGALIZATION BUT EVEN SO, TO “END THE WAR ON DRUGS” BY LEGALIZATION OF MJ WON’T DO IT
- WHAT WILL HAPPEN IS THE REDUCTION ON THE ARRESTS ANNUALLY (FOR POSSESSION) IN THE US – ABOUT 700,000 REDUCTION IN ARRESTS ANNUALLY
- HOW TO LEGALIZE? INDUSTRY – MAJORITY OF MARKET IS HEAVY USERS/ADDICTED– (80% OF VOLUME USED IS BY 20%)
- IF WE MAKE IT MORE AVAILABLE AND ACCESSIBLE, CHEAPER, REMOVE SOCIAL STIGMA AND LEGAL PENALTIES AND HAVE INDUSTRY AGGRESSIVELY ADVERTISING IT, USE WILL INCREASE
- POSSIBLE MJ COULD HAVE SUBTRACTIVE EFFECT ON ALC USE? DON’T KNOW. COULD USE BOTH?

“PROHIBITION DOESN'T WORK-  
EVERYBODY KNOWS THAT!”



SO, LEGALIZE, REGULATE, TAX, EDUCATE (“JUST LIKE ALCOHOL”)



JUST LIKE ALCOHOL ...

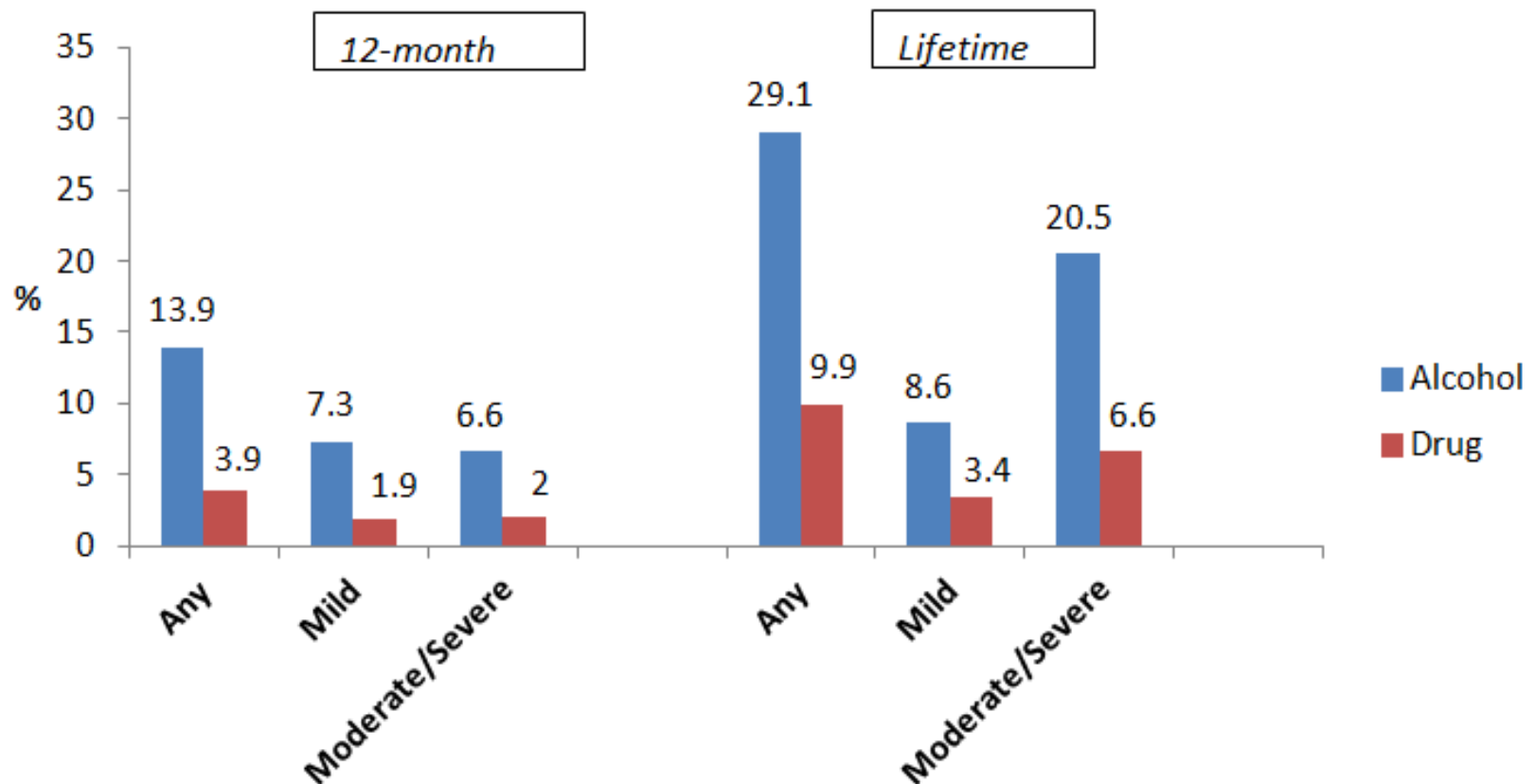
21<sup>ST</sup> AMENDMENT REPEALED ALCOHOL  
PROHIBITION... AND VIRTUALLY ENDED OUR  
ALCOHOL PROBLEMS (???)



# DSM-V Lifetime and 12-Month Prevalence of Alcohol and Drug Use Disorder

3-3.5x more addiction cases for alcohol in the past year/lifetime than ALL illicit drugs combined

12-month and Lifetime Prevalence of DSM-5 Alcohol and Drug Use Disorder



# ...DID ALCOHOL RE-LEGALIZATION PUT AN END TO OUR ALCOHOL PROBLEMS?

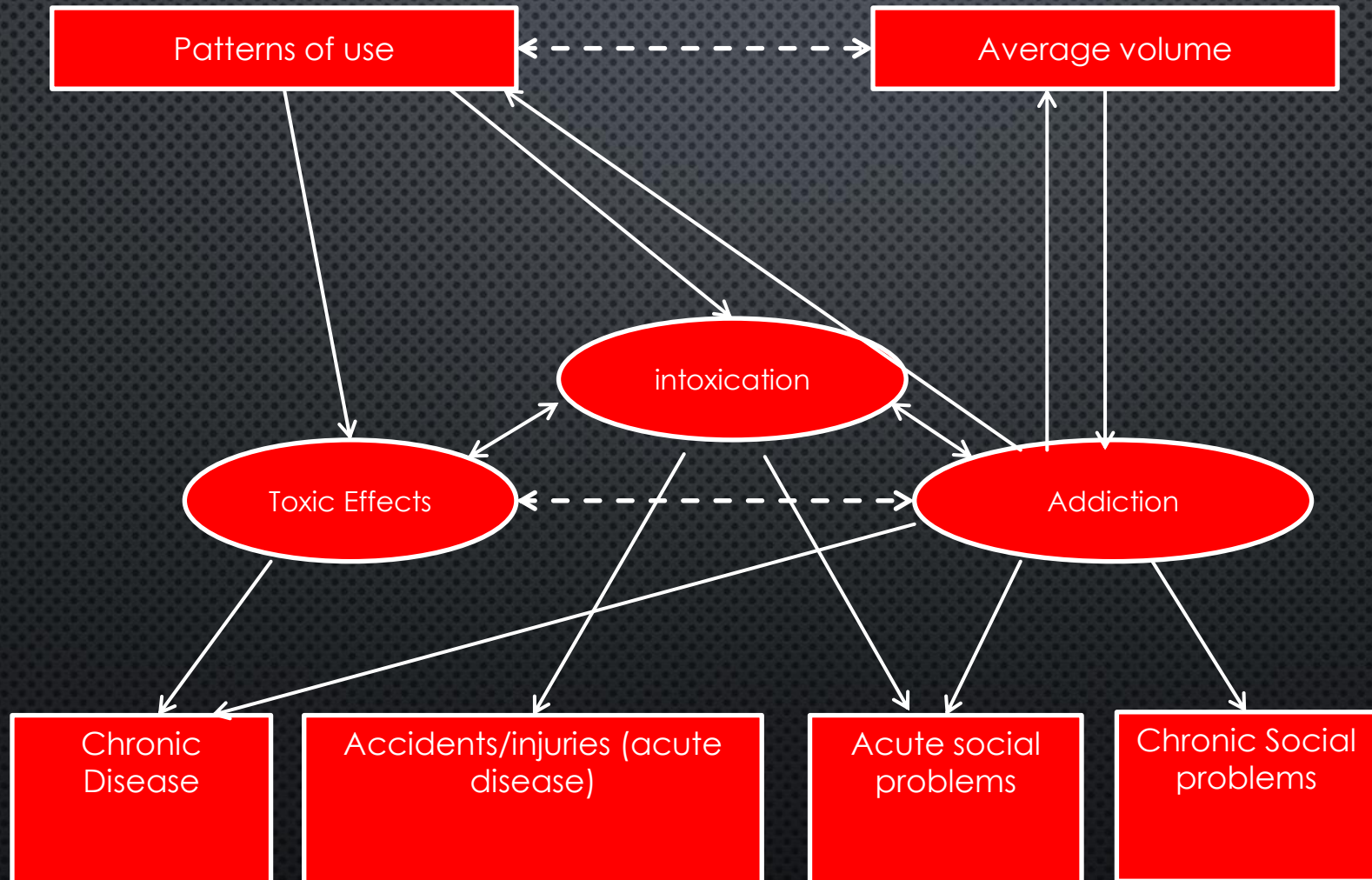
- ALCOHOL = ADDICTIVE DRUG - MAJORITY OF ADDICTED INDIVIDUALS IN US ARE ADDICTED TO ALCOHOL
- ALCOHOL = LEVEL I CARCINOGEN – KNOWN TO CAUSE CANCER
- 40 MILLION INDIVIDUALS DRINK AT RISKY/HARMFUL LEVELS
- 100,000 DEATHS DUE TO ALCOHOL ANNUALLY – 3<sup>RD</sup> LEADING CAUSE PREVENTABLE DEATH
- 10,000 KILLED EACH YEAR ON ROADS IN ALCOHOL-RELATED ACCIDENTS - HUNDREDS OF THOUSANDS MORE INJURED
- ALCOHOL-RELATED CRASHES COST TAXPAYERS \$100 BILLION; OVERALL ECONOMIC **BURDEN \$250 BILLION** (FED/STATE/LOCAL COMBINED TAX REVENUE FROM ALCOHOL SALES = \$15 BILLION)
- **3 MILLION ALCOHOL-RELATED ARRESTS** ANNUALLY (E.G., LIQUOR VIOLATIONS; UNDERAGE SALES; DRUNK AND DISORDERLY/VIOLENCE/DOMESTIC VIOLENCE); NEARLY 1.4 MILLION ARRESTED FOR DUI
- IF “PROHIBITION DOESN'T WORK” IT'S HARD TO MAKE THE CASE THAT LEGALIZATION IS THE SOLUTION...

# ALCOHOL AND HARM

- ON ALCOHOL CONTAINERS, WHY DON'T WE HAVE "ALCOHOL MAY CAUSE ADDICTION" OR "ALCOHOL CAUSES CANCER"?

# HOW COULD INCREASED USE OF MJ CAUSE HARM TO PUBLIC HEALTH AND PUBLIC SAFETY?

## Toxicity, Intoxication, and Addiction

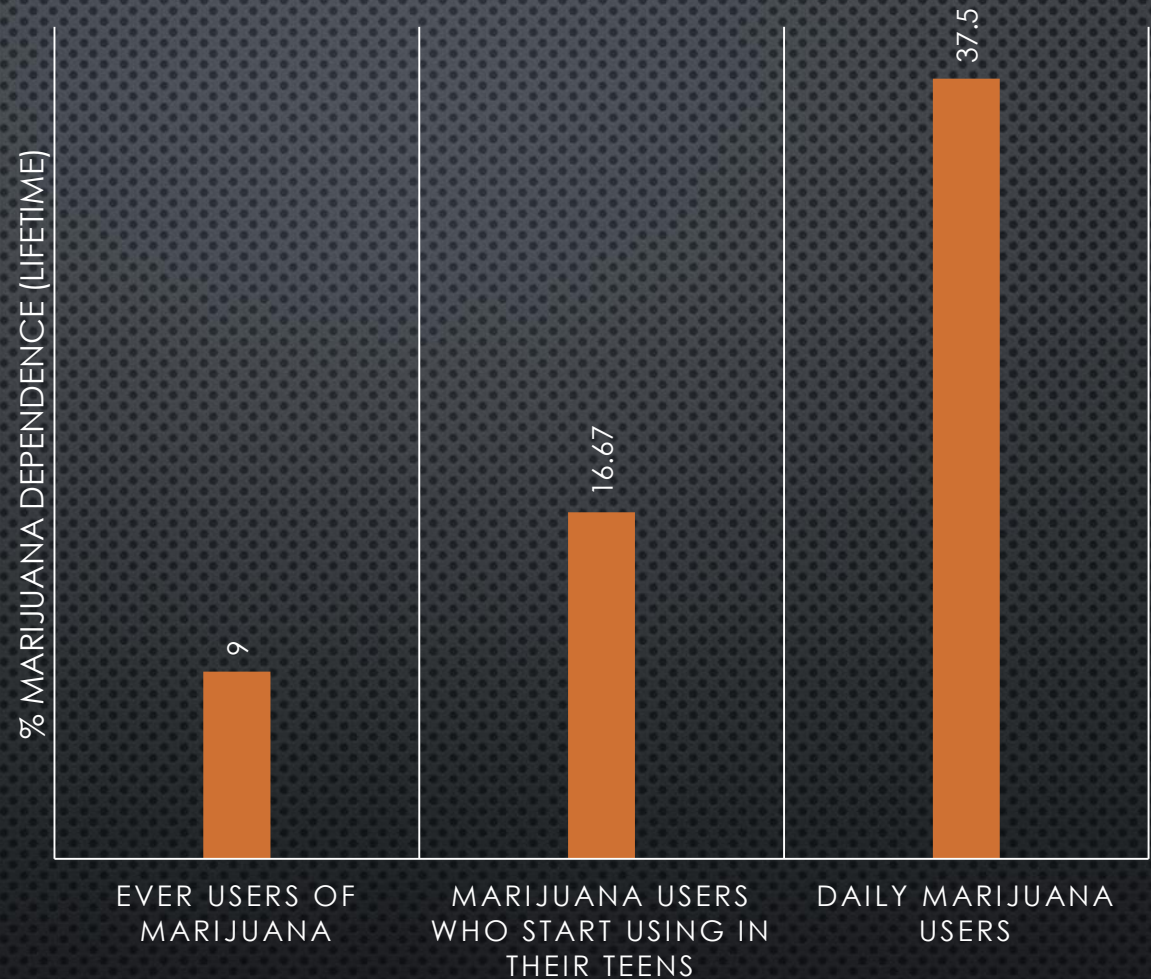




Addiction

# ADDICTIVENESS OF MARIJUANA

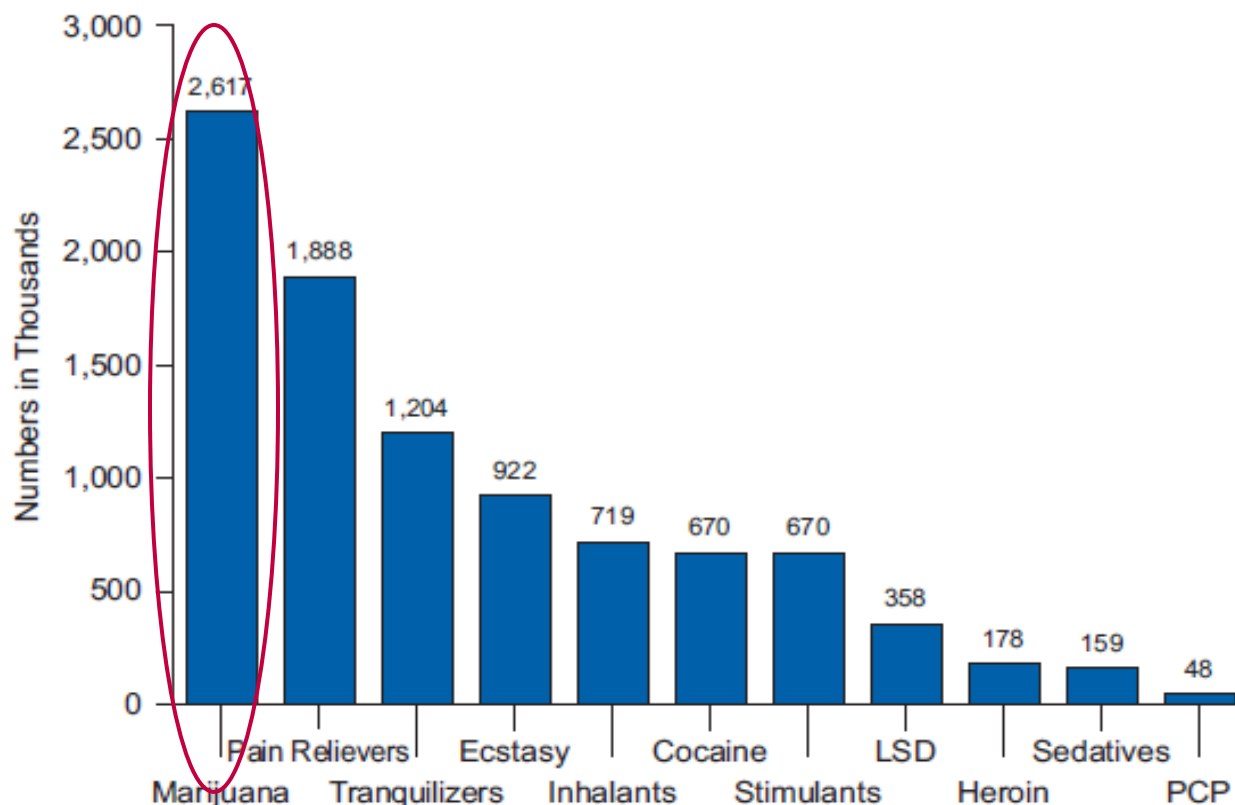
“ADOLESCENTS, ESPECIALLY TROUBLED ONES, AND PEOPLE WITH PSYCHIATRIC DISORDERS (INCLUDING SUBSTANCE ABUSE) APPEAR MORE LIKELY THAN THE GENERAL POPULATION TO BECOME DEPENDENT ON MARIJUANA...”



-- INSTITUTE OF MEDICINE

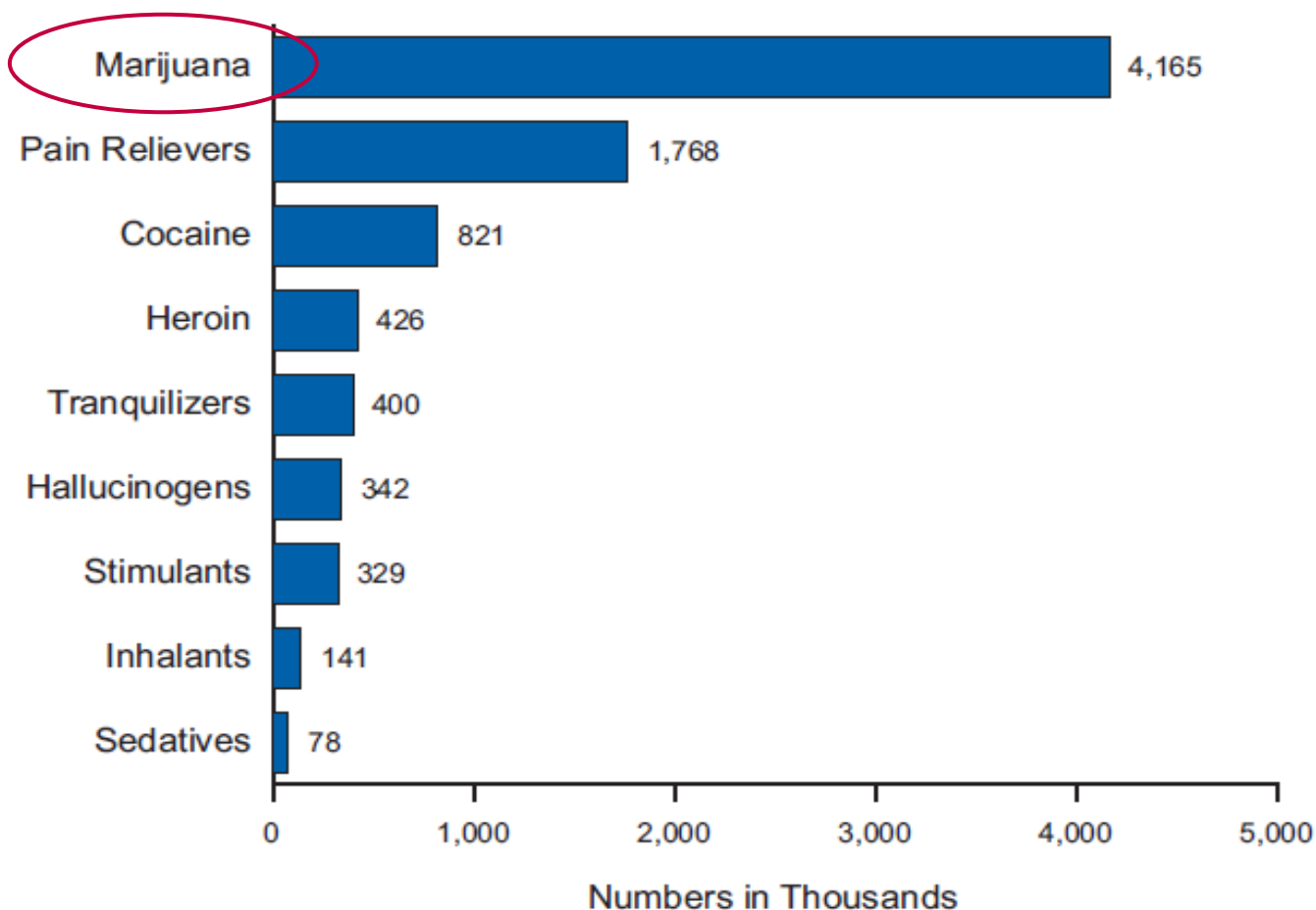
Anthony, J.; Warner, L.A.; and Kessler, R.C. *Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: Basic findings from the National Comorbidity Survey*. *Exp Clin Psychopharmacol* 2:244–268, 1994;  
Hall, W.; and Degenhardt, L. *Adverse health effects of non-medical cannabis use*. *Lancet* 374:1383–1391, 2009;  
Hall, W. *The adverse health effects of cannabis use: What are they, and what are their implications for policy?* *Int J of Drug Policy* 20:458–466, 2009

## PAST YEAR INITIATES OF SPECIFIC DRUGS UNITED STATES

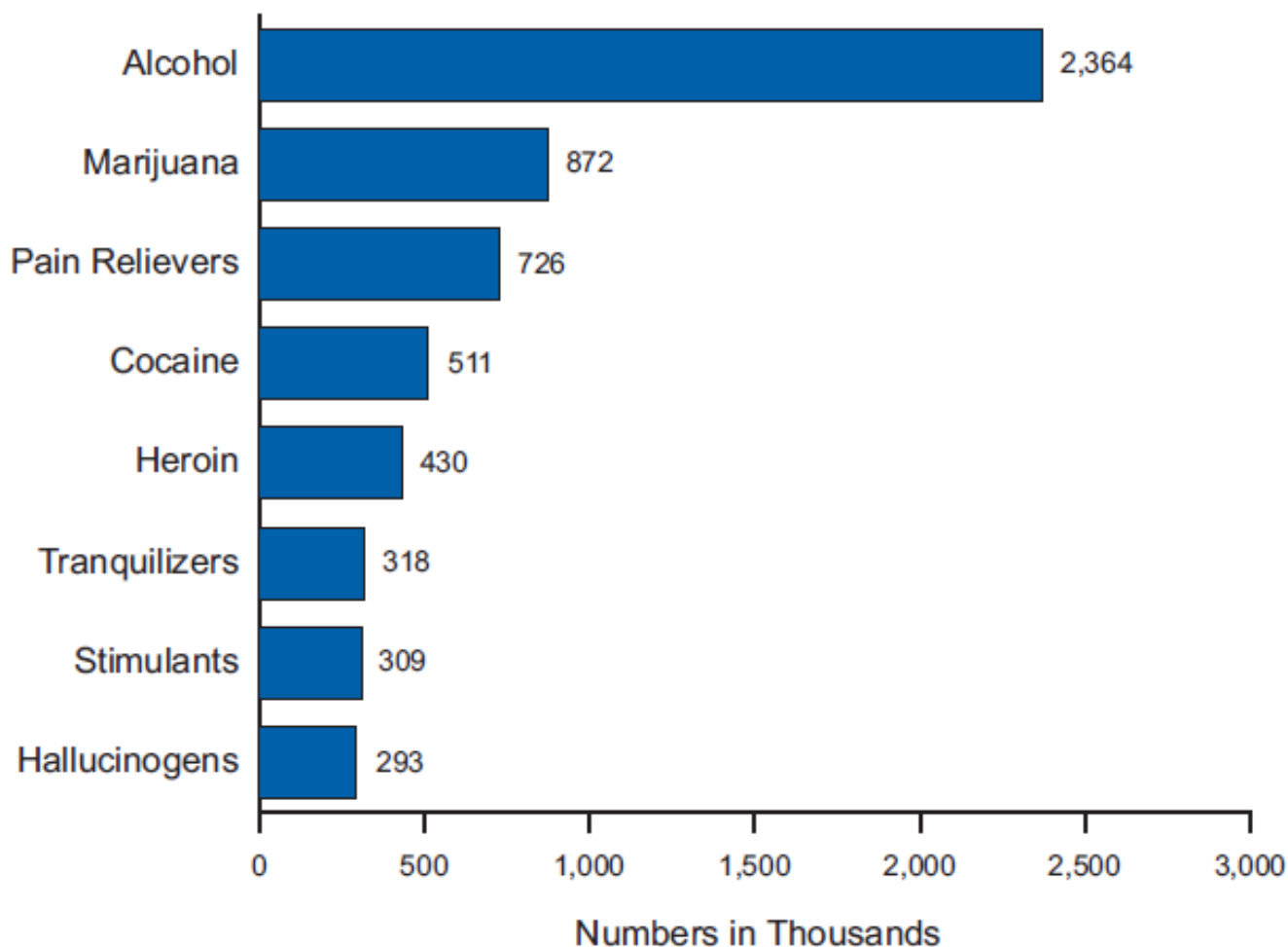


Note: Numbers refer to persons who used a specific drug for the first time in the past year, regardless of whether initiation of other drug use occurred prior to the past year.

**Figure 7.2 Specific Illicit Drug Dependence or Abuse in the Past Year among Persons Aged 12 or Older: 2011**



**Figure 7.8 Substances for Which Most Recent Treatment Was Received in the Past Year among Persons Aged 12 or Older: 2011**



# Prevalence of Marijuana Use Disorders in the United States Between 2001-2002 and 2012-2013

Deborah S. Hasin, PhD; Tulshi D. Saha, PhD; Bradley T. Kerridge, PhD; Risë B. Goldstein, PhD, MPH;  
S. Patricia Chou, PhD; Haitao Zhang, PhD; Jeeseun Jung, PhD; Roger P. Pickering, MS; W. June Ruan, MA;  
Sharon M. Smith, PhD; Boji Huang, MD, PhD; Bridget F. Grant, PhD, PhD

**IMPORTANCE** Laws and attitudes toward marijuana in the United States are becoming more permissive but little is known about whether the prevalence rates of marijuana use and marijuana use disorders have changed in the 21st century.

**OBJECTIVE** To present nationally representative information on the past-year prevalence rates of marijuana use, marijuana use disorder, and marijuana use disorder among marijuana users in the US adult general population and whether this has changed between 2001-2002 and 2012-2013.

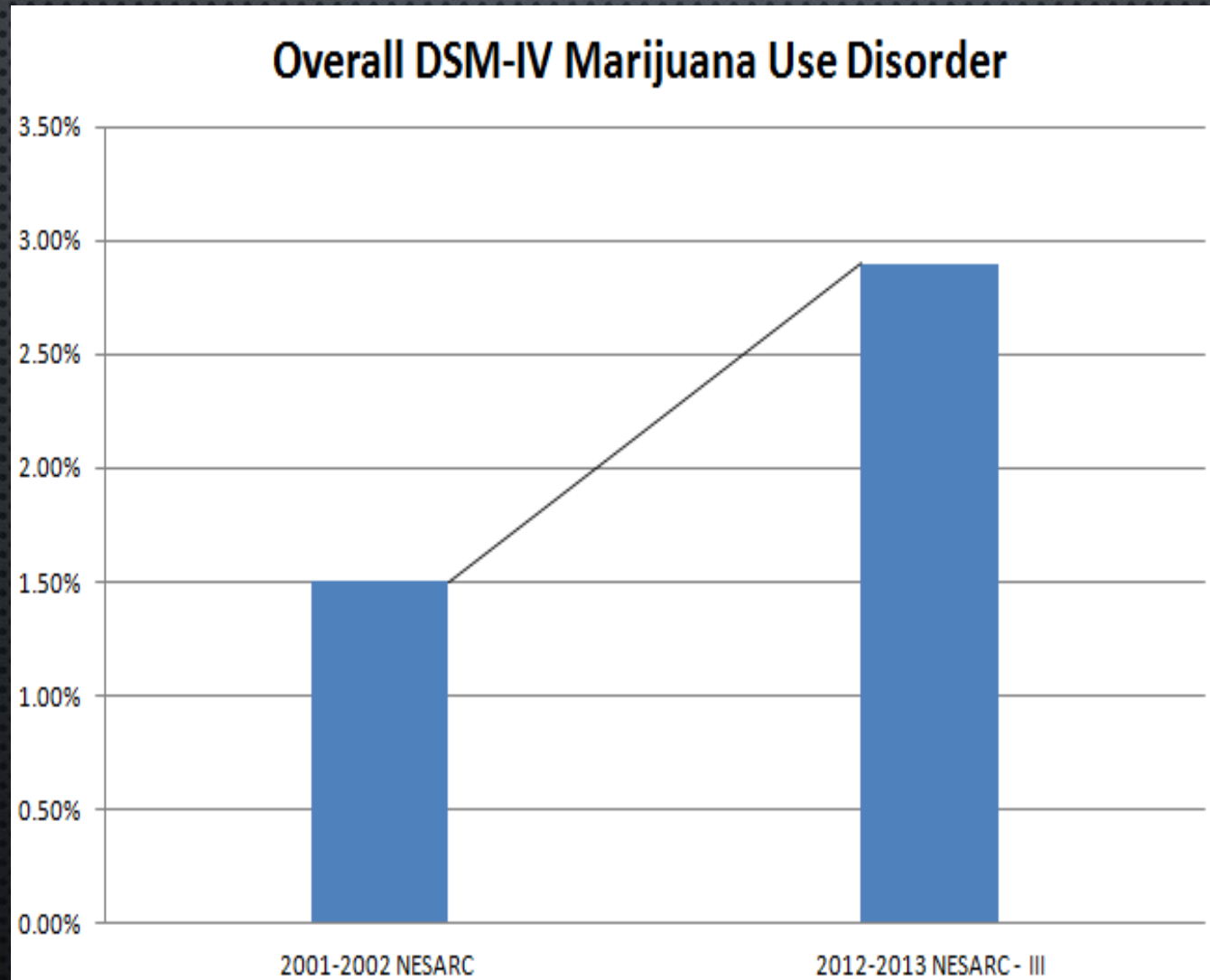
**DESIGN, SETTING, AND PARTICIPANTS** Face-to-face interviews conducted in surveys of 2 nationally representative samples of US adults: the National Epidemiologic Survey on Alcohol and Related Conditions (data collected April 2001-April 2002; N = 43 093) and the National Epidemiologic Survey on Alcohol and Related Conditions-III (data collected April 2012-June 2013; N = 36 309). Data were analyzed March through May 2015.


**MAIN OUTCOMES AND MEASURES** Past-year marijuana use and *DSM-IV* marijuana use disorder (abuse or dependence).

**RESULTS** The past-year prevalence of marijuana use was 4.1% (SE, 0.15) in 2001-2002 and 9.5% (SE, 0.27) in 2012-2013, a significant increase ( $P < .05$ ). Significant increases were also found across demographic subgroups (sex, age, race/ethnicity, education, marital status, income, urban/rural, and region). The past-year prevalence of *DSM-IV* marijuana use disorder was 1.5% (0.08) in 2001-2002 and 2.9% (SE, 0.13) in 2012-2013 ( $P < .05$ ). With few exceptions, increases in the prevalence of marijuana use disorder between 2001-2002 and 2012-2013 were also statistically significant ( $P < .05$ ) across demographic subgroups. However, the prevalence of marijuana use disorder among marijuana users decreased significantly from 2001-2002 (35.6%; SE, 1.37) to 2012-2013 (30.6%; SE, 1.04).

**CONCLUSIONS AND RELEVANCE** The prevalence of marijuana use more than doubled between 2001-2002 and 2012-2013, and there was a large increase in marijuana use disorders during that time. While not all marijuana users experience problems, nearly 3 of 10 marijuana users manifested a marijuana use disorder in 2012-2013. Because the risk for marijuana use disorder did not increase among users, the increase in prevalence of marijuana use disorder is owing to an increase in prevalence of users in the US adult population. Given changing laws and attitudes toward marijuana, a balanced presentation of the likelihood of adverse consequences of marijuana use to policy makers, professionals, and the public is needed.

# PAST YEAR *DSM-IV* MARIJUANA USE DISORDER



A red oval with a white border, centered on a dark gray background with a fine grid pattern.

Toxic  
Effects

# Residual Effects of Cannabis Use on Neurocognitive Performance After Prolonged Abstinence: A Meta-Analysis

Amy M. Schreiner and Michael E. Dunn  
University of Central Florida

Cannabis is the most widely used illicit drug in the U.S., and the number of illicit and licit users is rising. Lasting neurocognitive changes or deficits as a result of use are frequently noted despite a lack of clarity in the scientific literature. In an effort to resolve inconsistencies in the evidence of lasting residual effects of cannabis use, we conducted two meta-analyses. First, we updated a previous meta-analysis on broad



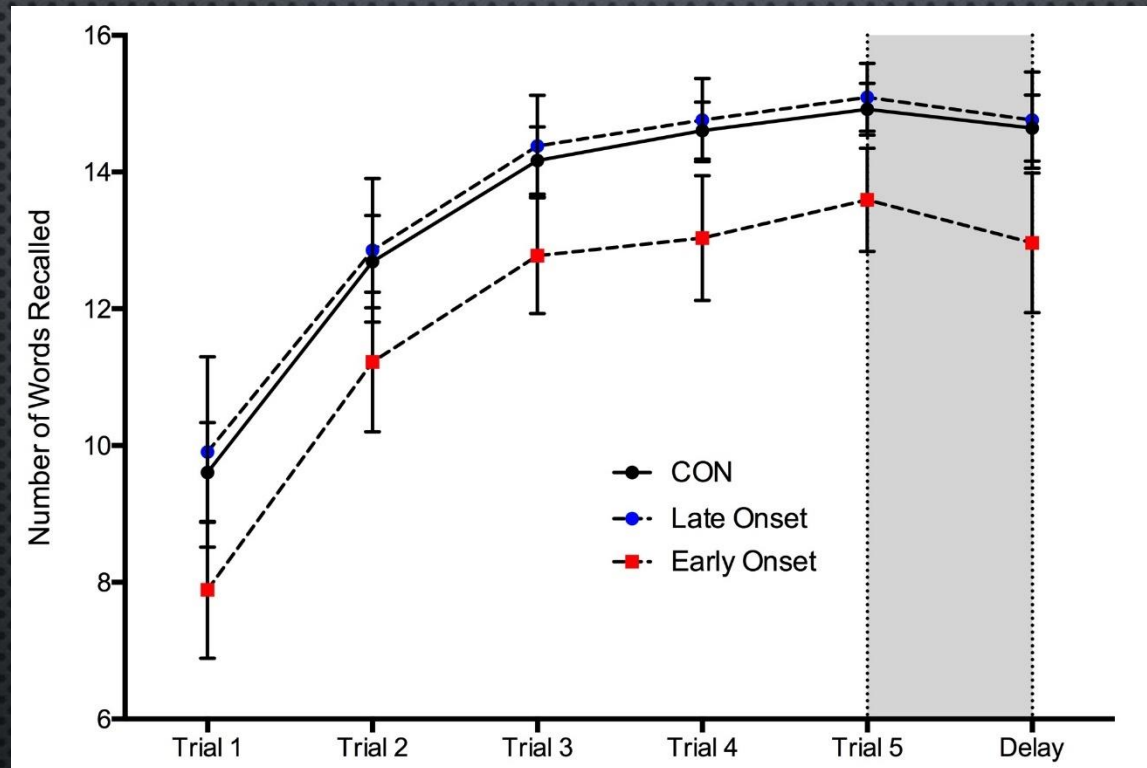
## 1. First Analysis (k=33)

Results: Neurocognitive deficits in most domains of functioning present early during abstinence

## 2. Second Sub-Analysis (k=13)

Results: Not present after 25 or more days of

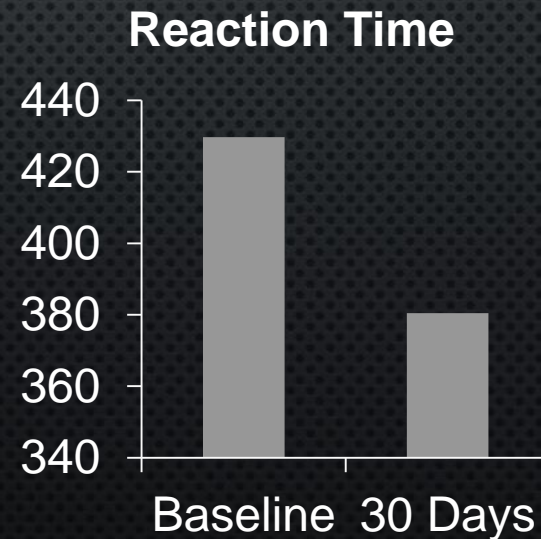
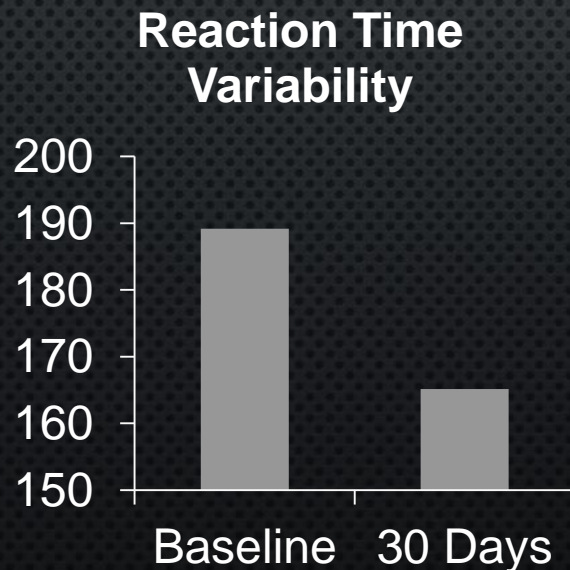
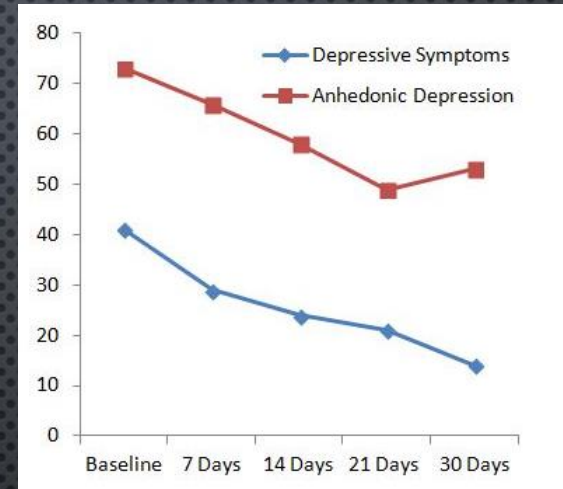
# Marijuana Users Show Worse Performance on a Memory Test

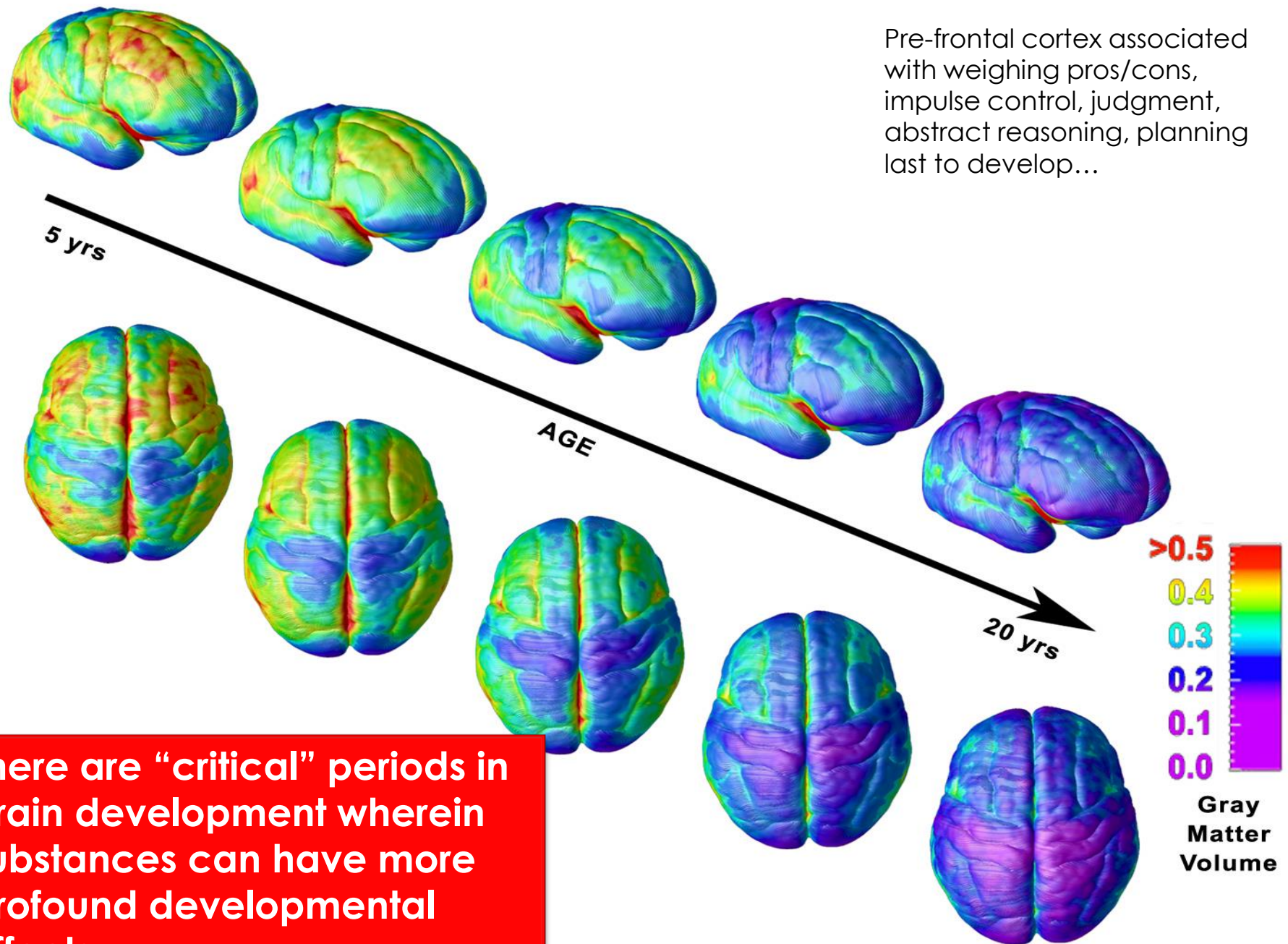


- MJ users, particularly early-onset users (<16), show impaired learning compared to non-users
- Could mean students using MJ regularly could have difficulty attending to and learning new information

# WHAT HAPPENS AFTER 30 DAYS OF ABSTINENCE?

- PSYCHIATRIC
  - IMPROVEMENT IN MOOD
- COGNITION
  - ↑ ATTENTION
  - ↑ EXECUTIVE FUNCTIONS





Pre-frontal cortex associated with weighing pros/cons, impulse control, judgment, abstract reasoning, planning last to develop...

There are “critical” periods in brain development wherein substances can have more profound developmental effects...

# IMPLICATIONS FOR LEGAL, COMMERCIALIZED RECREATIONAL USE

- IMPORTANT IMPLICATIONS BECAUSE CO JUST RELEASED LATEST REPORT ON MJ IMPACT AND FOUND THAT WHILE MJ USE NATIONALLY DECLINED 4% IN 2015 AMONG YOUTH, IT WENT UP 20% IN CO

# Persistent cannabis users show neuropsychological decline from childhood to midlife

Madeline H. Meier<sup>a,b,1</sup>, Avshalom Caspi<sup>a,b,c,d,e</sup>, Antony Ambler<sup>e,f</sup>, HonaLee Harrington<sup>b,c,d</sup>, Renate Houts<sup>b,c,d</sup>, Richard S. E. Keefe<sup>d</sup>, Kay McDonald<sup>f</sup>, Aimee Ward<sup>f</sup>, Richie Poulton<sup>f</sup>, and Terrie E. Moffitt<sup>a,b,c,d,e</sup>

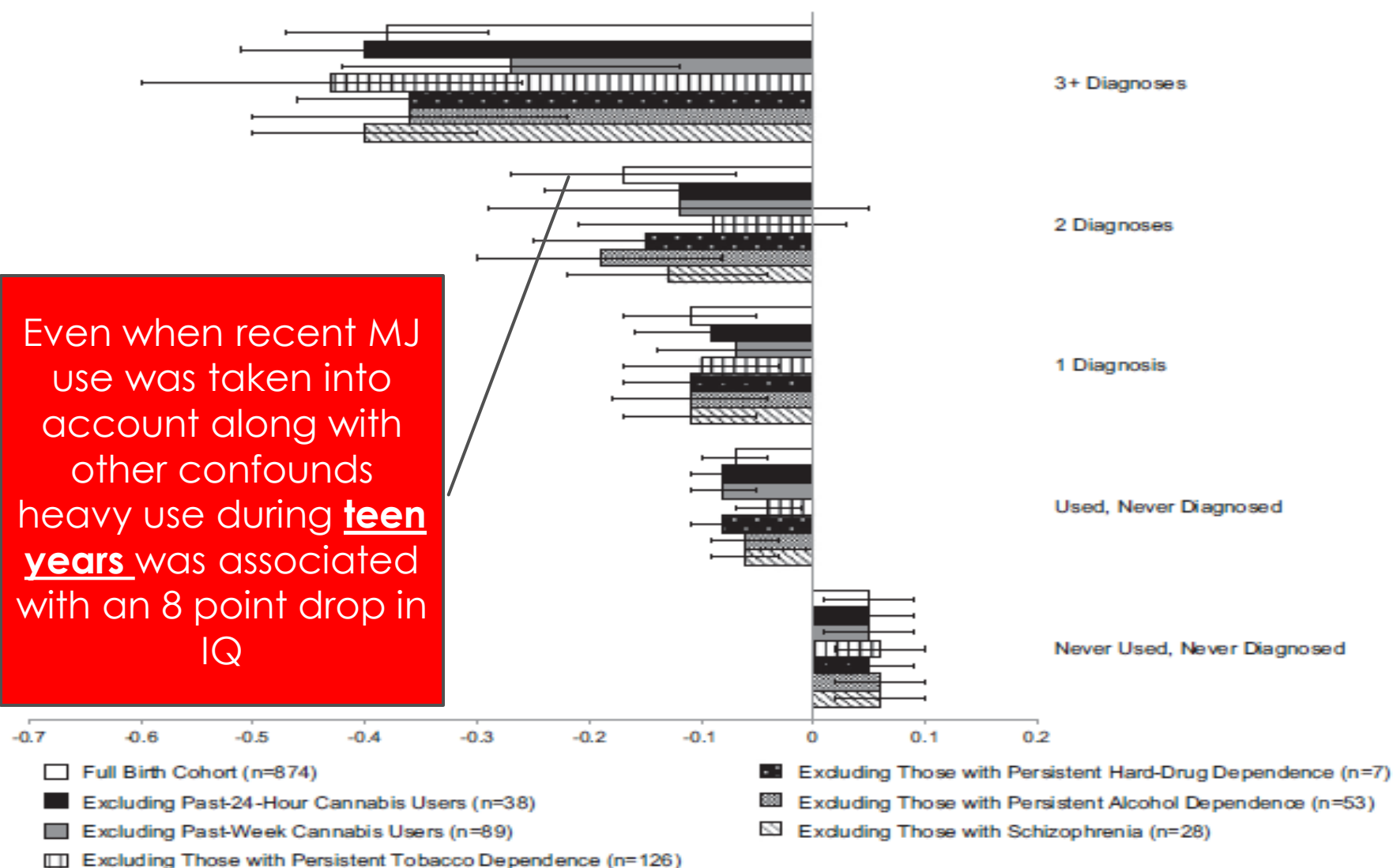
<sup>a</sup>Duke Transdisciplinary Prevention Research Center, Center for Child and Family Policy, <sup>b</sup>Department of Psychology and Neuroscience, and <sup>c</sup>Institute for Genome Sciences and Policy, Duke University, Durham, NC 27708; <sup>d</sup>Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710; <sup>e</sup>Social, Genetic, and Developmental Psychiatry Centre, Institute of Psychiatry, King's College London, London SE5 8AF, United Kingdom; and <sup>f</sup>Dunedin Multidisciplinary Health and Development Research Unit, Department of Preventive and Social Medicine, School of Medicine, University of Otago, Dunedin 9054, New Zealand

Edited by Michael I. Posner, University of Oregon, Eugene, OR, and approved July 30, 2012 (received for review April 23, 2012)

**Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants**

**neuropsychological test performance after a period of abstinence from cannabis. There are two commonly cited potential limitations of this approach. One is the absence of data on initial, precannabis-use neuropsychological functioning. It is possible that differences in test performance between cannabis users and controls are attributable to premorbid rather than cannabis-induced deficits (17–20). A second limitation is re-**

Even when recent MJ use was taken into account along with other confounds heavy use during teen years was associated with an 8 point drop in IQ



**Fig. 1.** Ruling out alternative explanations. Shown is change in full-scale IQ (in SD units) from childhood to adulthood as a function of the number of study waves between ages 18 y and 38 y for which a study member met criteria for cannabis dependence. Change scores are presented for the full birth cohort and the cohort excluding (i) past 24-h cannabis users, (ii) past-week cannabis users, (iii) those with persistent tobacco dependence, (iv) those with persistent hard-drug dependence, (v) those with persistent alcohol dependence, and (vi) those with lifetime schizophrenia. Persistent tobacco, hard-drug, and alcohol dependence were each defined as dependence at three or more study waves. IQ decline could not be explained by other factors. Error bars = SEs.

sizes, representing within-person IQ change as a function of tobacco, hard-drug, or alcohol dependence), and schizophrenia



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Associate editor: S. Andersen

## Cannabis and adolescent brain development



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### ARTICLE INFO

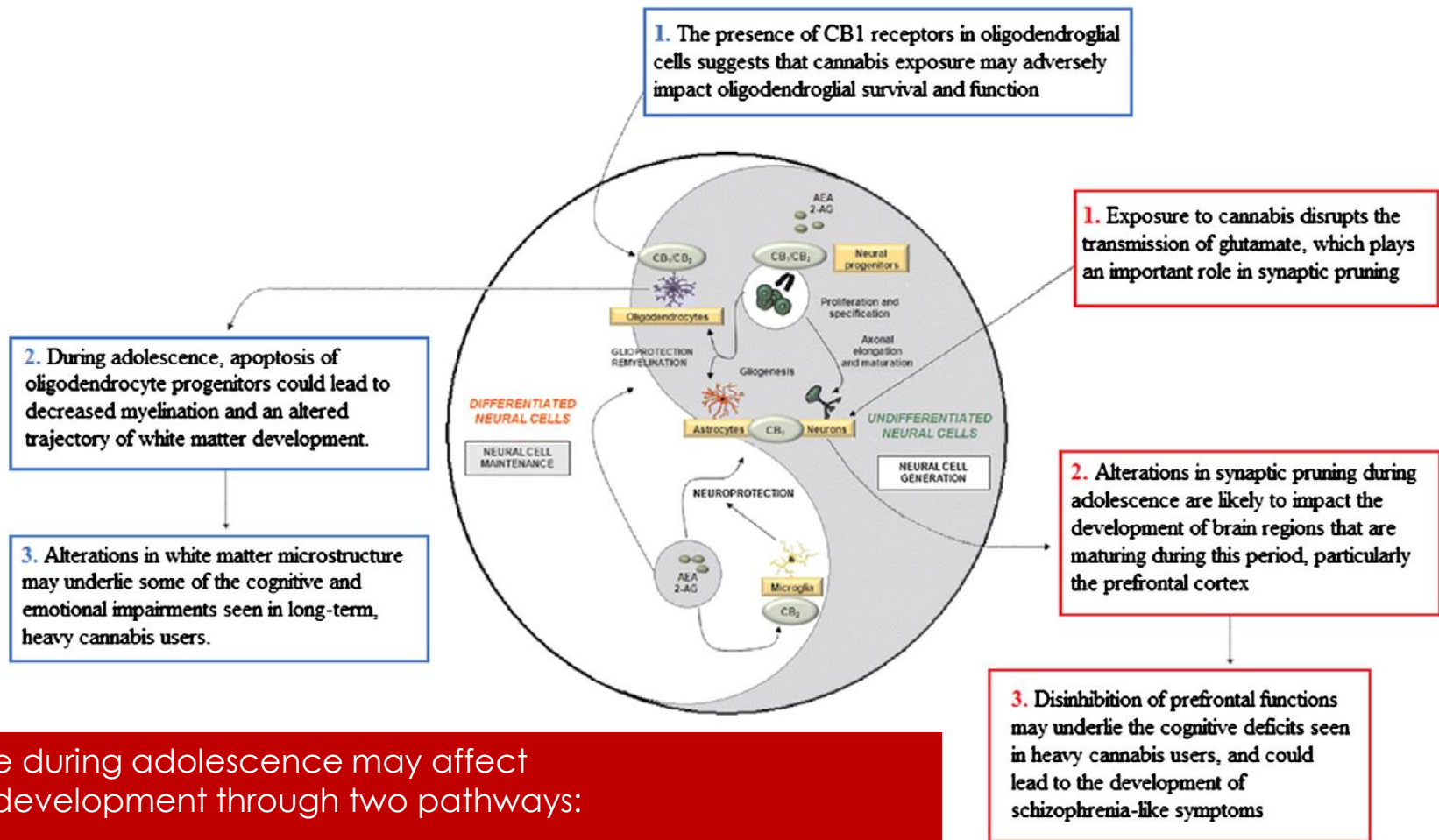
Available online 20 November 2014

#### Keywords:

Cannabis  
Adolescence  
Brain development  
Endocannabinoid  
Cognition  
Mental illness

### ABSTRACT

Heavy cannabis use has been frequently associated with increased rates of mental illness and cognitive impairment, particularly amongst adolescent users. However, the neurobiological processes that underlie these associations are still not well understood. In this review, we discuss the findings of studies examining the acute and chronic effects of cannabis use on the brain, with a particular focus on the impact of commencing use during adolescence. Accumulating evidence from both animal and human studies suggests that regular heavy use during this period is associated with more severe and persistent negative outcomes than use during adulthood, suggesting that the adolescent brain may be particularly vulnerable to the effects of cannabis exposure. As the endocannabinoid system plays an important role in brain development, it is plausible that prolonged use during adolescence results in a disruption in the normative neuromaturational processes that occur during this period. We identify synaptic pruning and white matter development as two processes that may be adversely impacted by cannabis exposure during adolescence. Potentially, alterations in these processes may underlie the cognitive and emotional deficits that have been associated with regular use commencing during adolescence.



MJ use during adolescence may affect Brain development through two pathways:

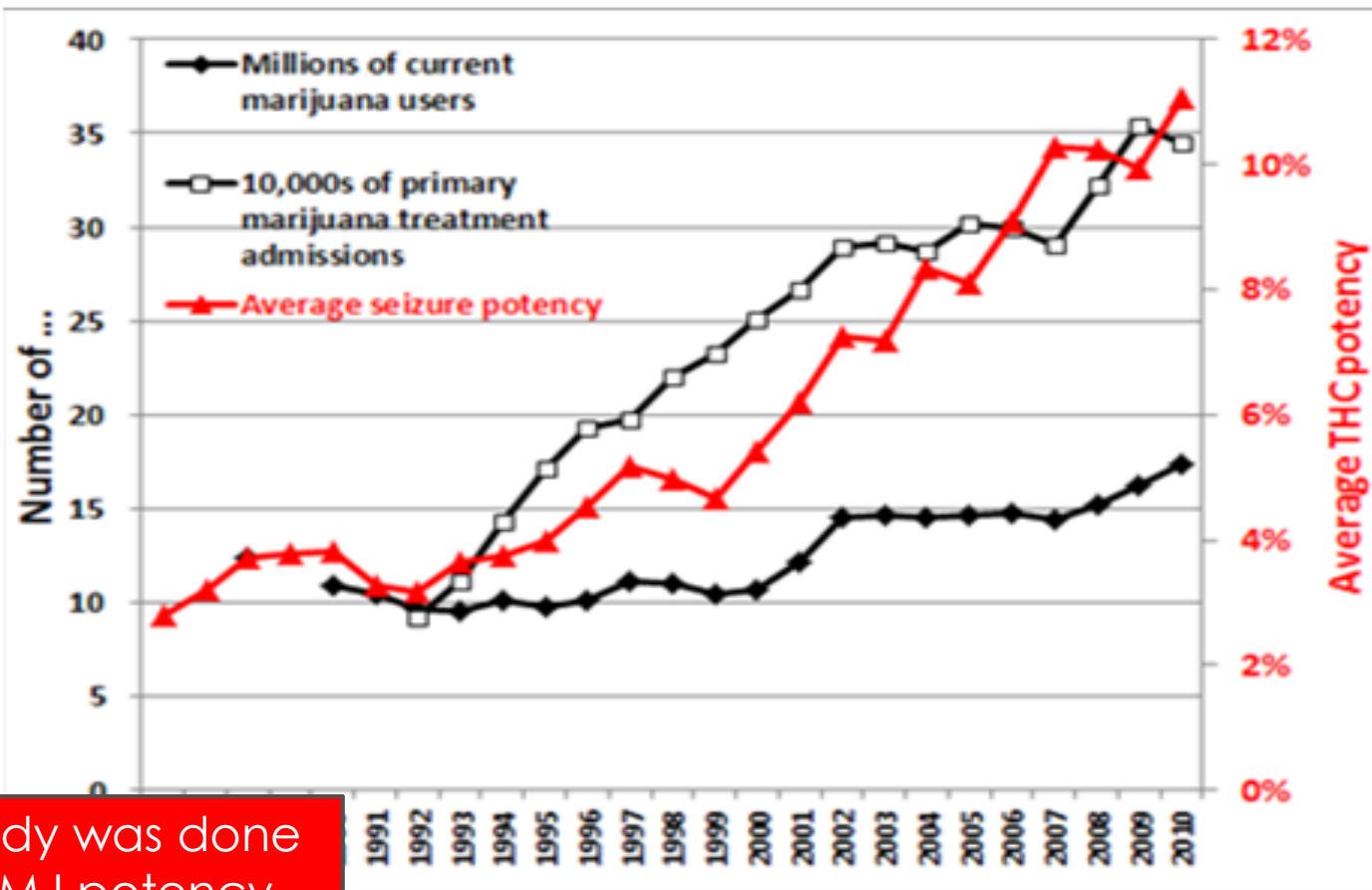
**1. Alters synaptic pruning** (via disrupting glutamate Transmission) leading to greater disinhibition in prefrontal regions leading to psychotic symptoms

**2. Decreased myelination altering development of white matter** leading to cognitive-emotional impairments

cells during prenatal and early post-natal stages of brain development (grey/yang side) as neuronal migration and axonal pathfinding, as well as the generation of glial cells, including functions of the endocannabinoid system and alter brain development: (i) by interfering

What will be the effects of higher potency MJ?

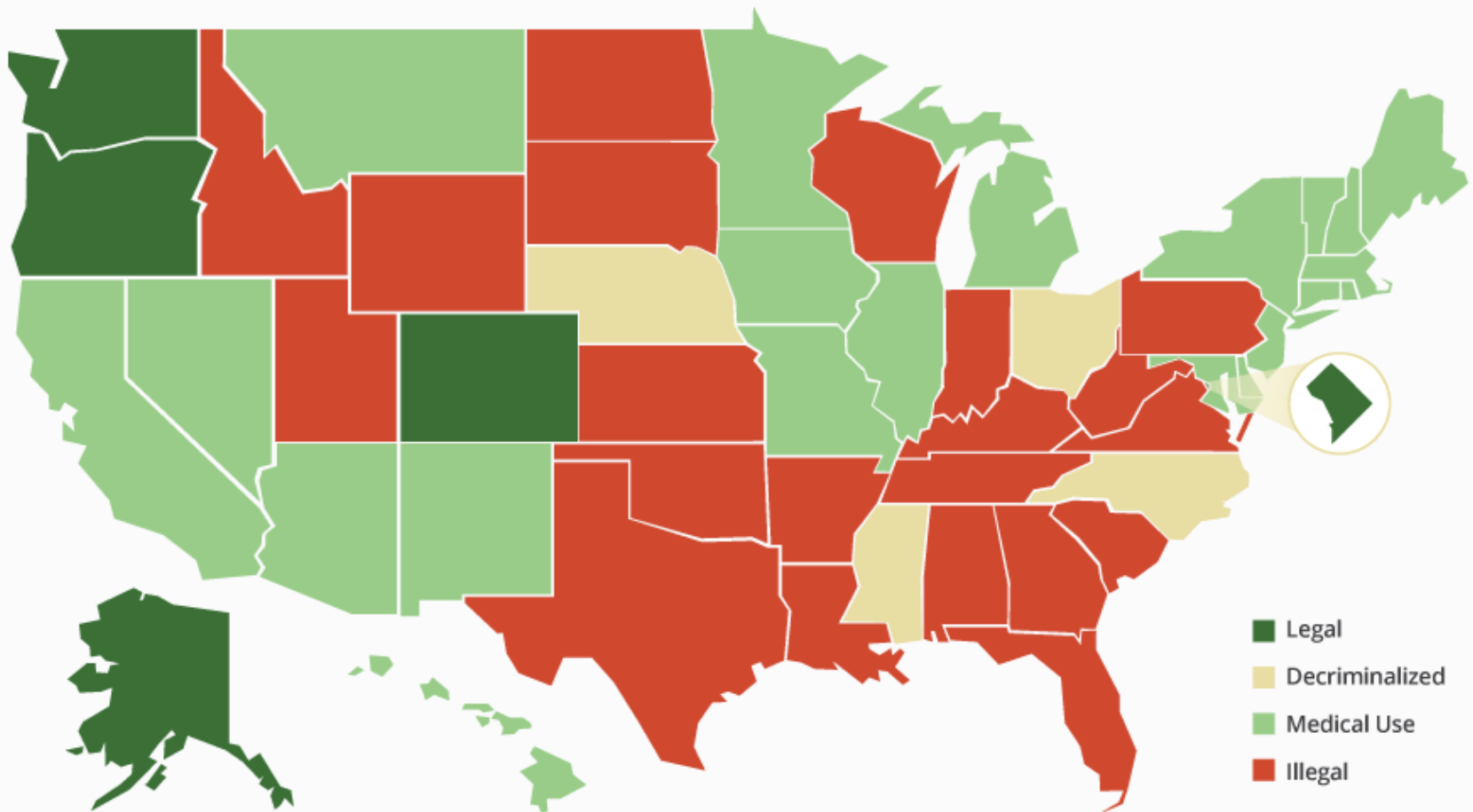
***MARIJUANA USERS, TREATMENT ADMISSIONS, AND AVERAGE POTENCY:  
1986-2010***



Sources: [NSDUH](#), [TEDS](#), National Seizure System

That study was done  
when MJ potency  
was lower....  
Increased potency in  
past 20 years

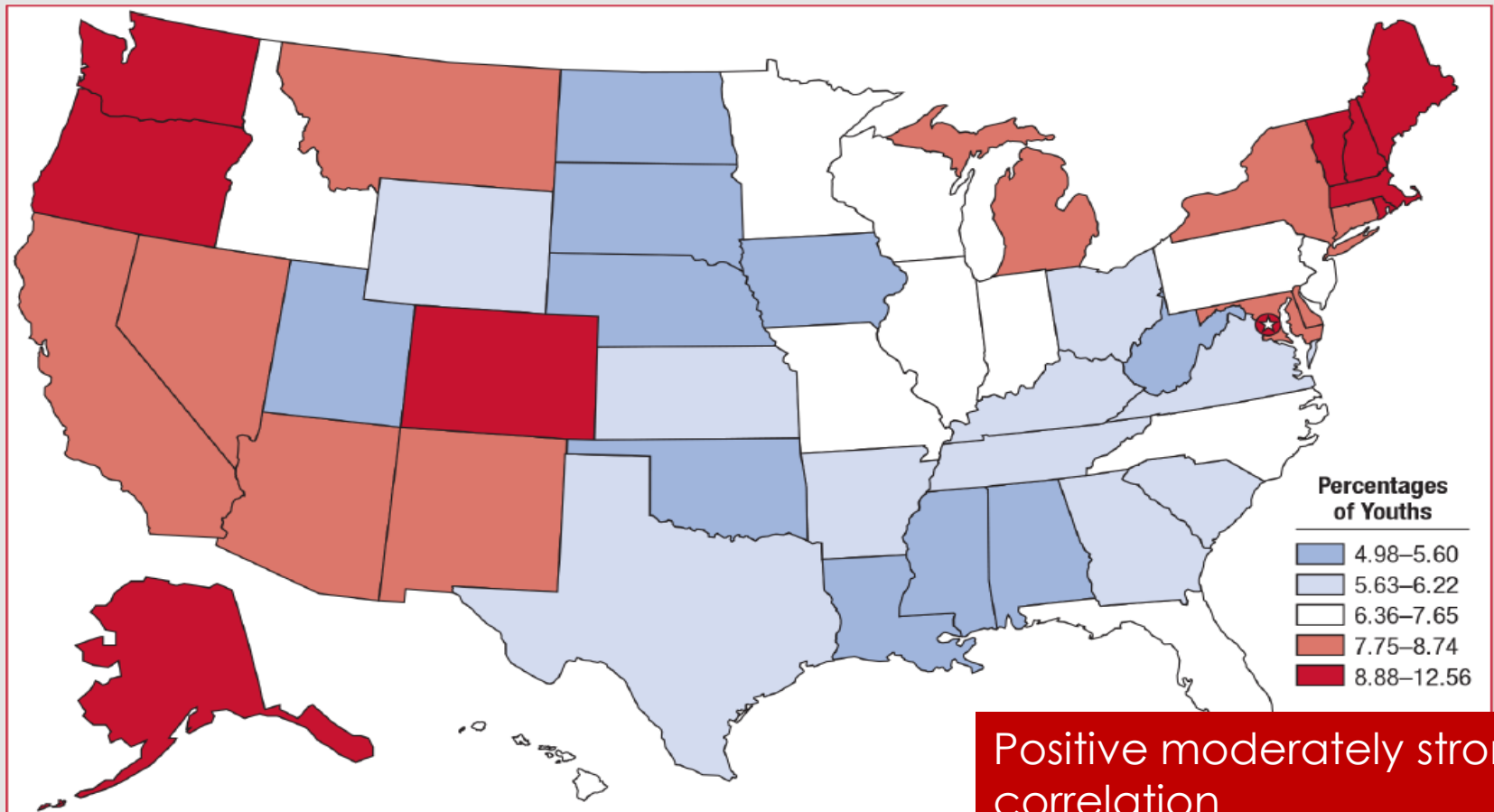
# Legality of Marijuana in the United States



Source: <http://www.economist.com/blogs/graphicdetail/2015/01/daily-chart-11>

DrugTreatment.com

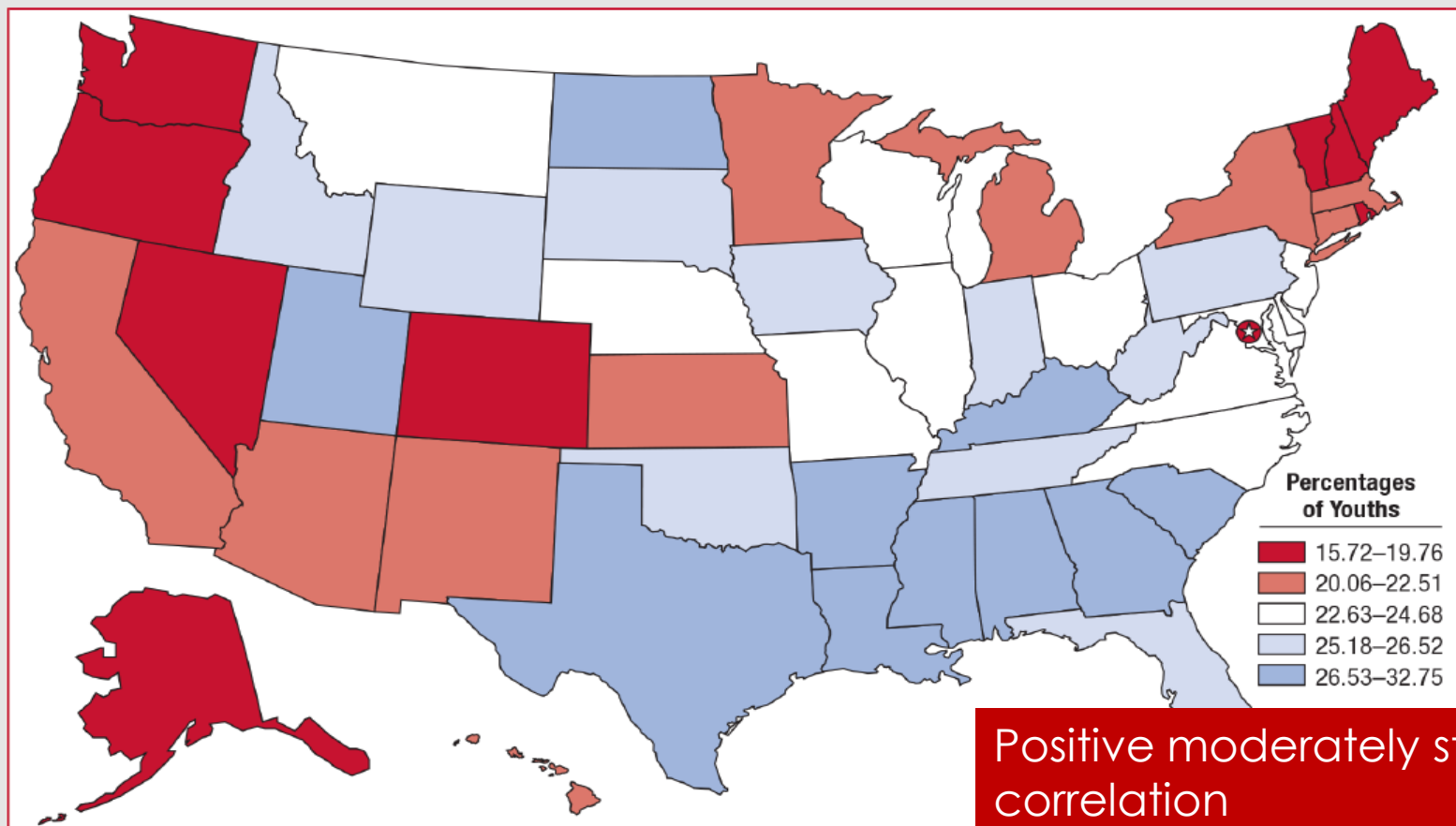
**Figure 1. Marijuana use in the past month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014**



Source: SAMHSA, Center for Behavioral Health Statistics and Research, National Survey on Drug Use and Health (NSDUHs), 2013 and 2014.

Positive moderately strong correlation across states, between higher rates of teenage use and legalization and “medicalization” of MJ

**Figure 2. Perceptions of great risk of harm from smoking marijuana once a month among youths aged 12 to 17, by state: percentages, annual averages, 2013-2014**



Source: SAMHSA, Center for Behavioral Health Statistics and Research, National Survey on Drug Use and Health (NSDUHs), 2013 and 2014.

Positive moderately strong correlation across states, between less perceived harm and legalization and “medicalization” of MJ

# IMPACT OF EDIBLES?



## Kids and Marijuana Edibles: A Worrisome Trend Emerges

Experts say states should mandate child-resistant packaging.

**E**Ds are seeing a surge in the number of young children having adverse reactions to marijuana. In three-quarters of the cases reported from 2000 through 2013, the children were younger than three years old, ages when children tend to explore their environment by mouth. Most children ate items found in their homes, such as brownies, cookies, candy, and other foods spiked with marijuana.

“A typical adult serving size for a marijuana edible often is a quarter of a brownie, but a small child eats an entire brownie and ends up in the [ED],” says Sarah Ramsay, nurse manager at the Rocky Mountain Poison and Drug Center in Denver.

Data from the National Poison Data System show that the rate of marijuana exposure among children younger than six in the United States rose 147.5% from 2006 to 2013, particularly in states where medical marijuana use is legal.

From 2000 to 2013, poison control centers received reports on 1,969 children younger than six who were exposed to marijuana. Boys and girls were affected equally. Almost half (48%) of ex-



Photo by Jeff Chiu / Associated Press.

NATIONAL POISONING SYSTEM  
DATA SHOW THAT MJ  
EXPOSURE AMONG KIDS <6YRS  
ROSE 148% FROM 2006-  
2013, PARTICULARLY IN STATES  
WHERE MED MJ IS LEGAL

high concentrations of the drug's \_\_\_\_\_ give a marijuana edible to a child

# Pediatric Marijuana Exposures in a Medical Marijuana State

George Sam Wang, MD; Genie Roosevelt, MD, MPH; Kennon Heard, MD

← Editorial pages 600 and 602

**IMPORTANCE** An increasing number of states are decriminalizing the use of medical marijuana, and the effect on the pediatric population has not been evaluated.

**OBJECTIVE** To compare the proportion of marijuana ingestions by young children who sought care at a children's hospital in Colorado before and after modification of drug enforcement laws in October 2009 regarding medical marijuana possession.

**DESIGN** Retrospective cohort study from January 1, 2005, through December 31, 2011.

**SETTING** Tertiary-care children's hospital emergency department in Colorado.

**PARTICIPANTS** A total of 1378 patients younger than 12 years evaluated for unintentional ingestions: 790 patients before September 30, 2009, and 588 patients after October 1, 2009.

**MAIN EXPOSURE** Marijuana ingestion.

**MAIN OUTCOMES AND MEASURES** Marijuana exposure visits, marijuana source, symptoms, and patient disposition.

**RESULTS** The proportion of ingestion visits in patients younger than 12 years (age range, 8 months to 12 years) that were related to marijuana exposure increased after September 30, 2009, from 0 of 790 (0%; 95% CI, 0%-0.6%) to 14 of 588 (2.4%; 95% CI, 1.4%-4.0%) ( $P < .001$ ). Nine patients had lethargy, 1 had ataxia, and 1 had respiratory insufficiency. Eight patients were admitted, 2 to the intensive care unit. Eight of the 14 cases involved medical marijuana, and 7 of these exposures were from food products.

**CONCLUSIONS AND RELEVANCE** We found a new appearance of unintentional marijuana ingestions by young children after modification of drug enforcement laws for marijuana possession in Colorado. The consequences of unintentional marijuana exposure in children should be part of the ongoing debate on legalizing marijuana.

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**Table 1. Demographics of Patients Seen in the Children's Hospital Emergency Department for Ingestions<sup>a</sup>**

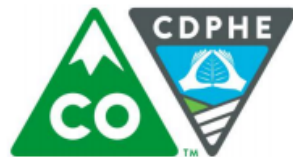
| Characteristic       | January 1, 2005,<br>Through September 30,<br>2009 | October 1, 2009,<br>Through December 31,<br>2011 |
|----------------------|---|--|
| No. of patients      | 790   | 588  |
| Age, median (IQR), y | 2.6 (1.6-3.0)                                     | 2.3 (1.5-3.6)                                    |
| Male sex             | 449 (56.8)  | 334 (56.8)                                       |
| Types of ingestions  |   |  |
| Acetaminophen        | 90 (11.3)   | 48 (8.2)   |
| Antihistamine        | 43 (5.4)  | 32 (5.4)   |
| Antidepressant       | 23 (2.9)  | 14 (2.3)   |
| Antitussive          | 18 (2.2)  | 14 (2.3)   |
| Marijuana exposures  | 0   | 14 (2.3)   |

New increase in unintentional marijuana ingestions by young children (e) unless otherwise noted.

Opposite trend to all other toxic ingestions

# Monitoring Health Concerns Related to Marijuana in Colorado: 2014

Changes in Marijuana Use Patterns,  
Systematic Literature Review, and  
Possible Marijuana-Related Health Effects



**COLORADO**

Department of Public  
Health & Environment

**Figure 1. Rates of Hospitalizations (HD) and Emergency Department (ED) Visits with Possible Marijuana Exposures<sup>a</sup> in Children Up to 9 Years per 100,000 HD and ED Visits in Children Under 9 Years Old by Time Period in Colorado.**

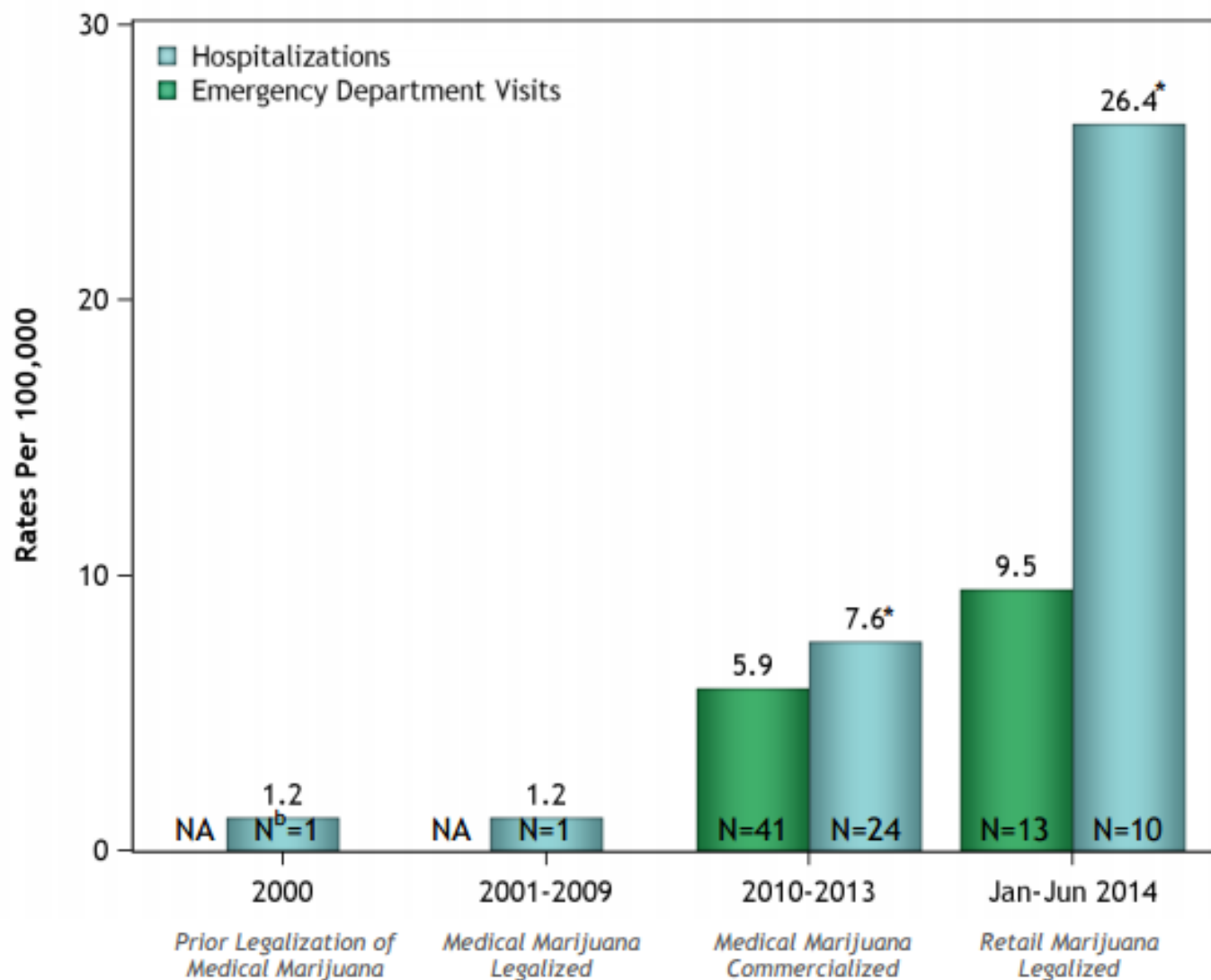
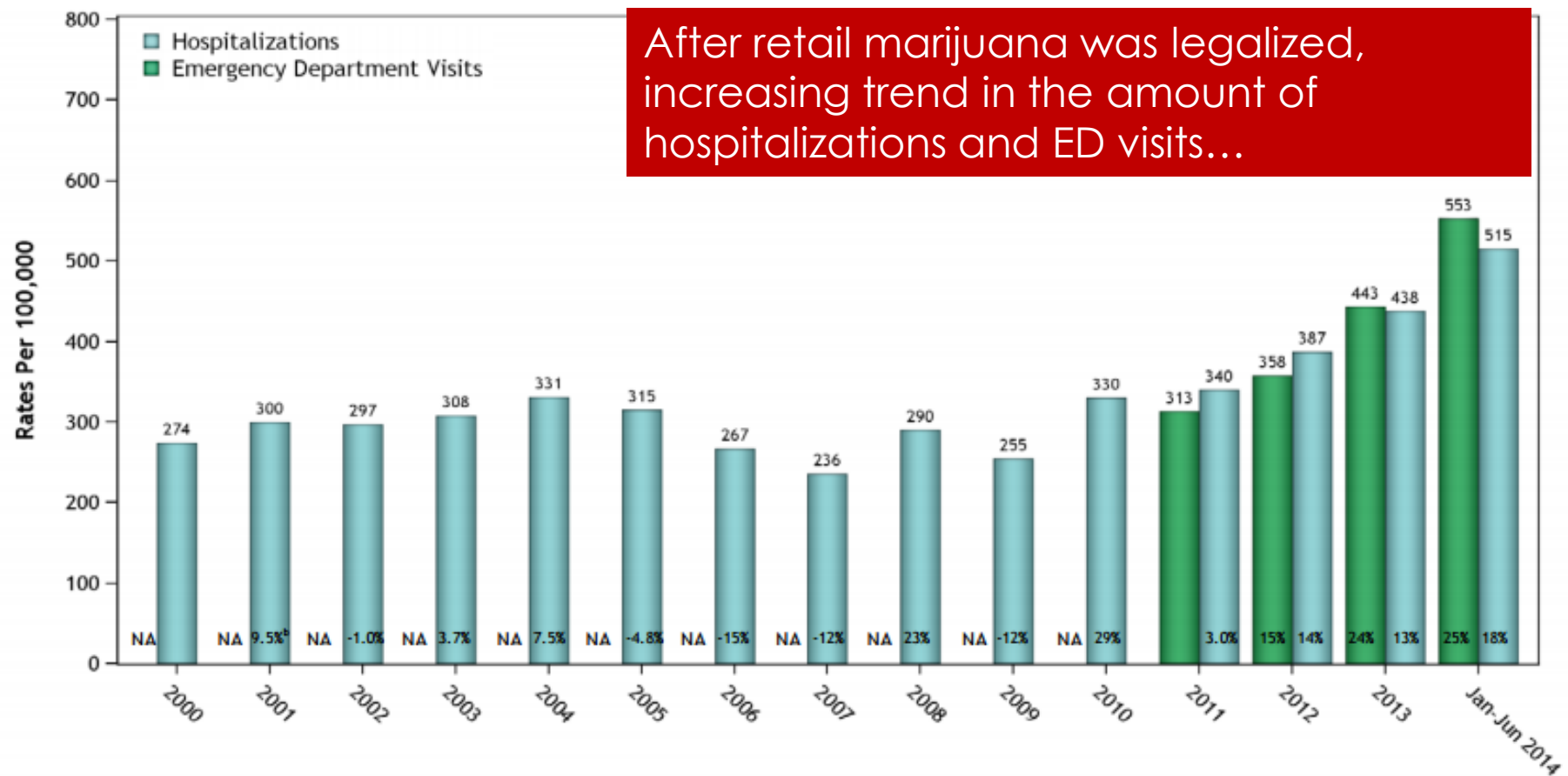


Figure 3. Rates of Hospitalizations (HD) and Emergency Department (ED) Visits with Possible Marijuana Exposures, Diagnoses, or Billing Codes<sup>a</sup> in the First Three Diagnosis Codes per 100,000 HD and ED Visits by Year in Colorado.



## Review

## Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review

Nora D. Volkow, MD; James M. Swanson, PhD; A. Eden Evins, MD; Lynn E. DeLisi, MD; Madeline H. Meier, PhD; Raul Gonzalez, PhD; Michael A. P. Bloomfield, MRCPsych; H. Valerie Curran, PhD; Ruben Baler, PhD

With a political debate about the potential risks and benefits of cannabis use as a backdrop, the wave of legalization and liberalization initiatives continues to spread. Four states (Colorado, Washington, Oregon, and Alaska) and the District of Columbia have passed laws that legalized cannabis for recreational use by adults, and 23 others plus the District of Columbia now regulate cannabis use for medical purposes. These policy changes could trigger a broad range of unintended consequences, with profound and lasting implications for the health and social systems in our country. Cannabis use is emerging as one among many interacting factors that can affect brain development and mental function. To inform the political discourse with scientific evidence, the literature was reviewed to identify what is known and not known about the effects of cannabis use on human behavior, including cognition, motivation, and psychosis.

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Published online February 3, 2016.

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It is well established that cannabis use causes acute impairment in the ability of the brain to hold information (ie, cognitive capacity). Hence, temporary deficits occur in learning and memory, attention, and working memory.

## Does Cannabis Use Affect Cognitive Capacity?

Cannabis use causes acute impairment of learning and memory, attention, and working memory,<sup>1-3</sup> but it is less clear if cannabis use is associated with enduring neuropsychological impairment. Case-control studies comparing nonintoxicated heavy cannabis users with nonusers have fairly consistently shown that heavy cannabis users perform worse on neuropsychological tests. For example, the results from 2 separate meta-analyses<sup>4,5</sup> showed that compared with nonusers, nonintoxicated cannabis users perform worse on measures of global neuropsychological function, with effect sizes for specific neuropsychological domains (executive functions, attention, learning and memory, motor skills, and verbal abilities) of approximately one-third of a standard deviation or less. When analyses in the second meta-analysis<sup>5</sup> were limited to 13 studies of cannabis users with at least 1 month of abstinence, there was no discernible difference between cannabis users and nonusers on neuropsychological test performance, suggesting that neuropsychological functions might recover with prolonged abstinence. Evidence suggests that the magnitude of neuropsychological impairment and the extent to which it persists after abstinence may depend on the frequency and duration of cannabis use, length of abstinence, and age at onset of use.<sup>6</sup>

Emerging evidence suggests that adolescents may be particularly vulnerable to the adverse effects of cannabis use. Adolescence represents a critical neurodevelopmental period characterized by marked synaptic pruning and increased myelination.<sup>7</sup>

Moreover, the endocannabinoid system appears to be involved in the regulation of key neurodevelopmental processes,<sup>7</sup> suggesting that the introduction of exogenous cannabinoids during adolescence could disrupt normal brain development. Animal research supports the possibility that adolescence represents a period of heightened vulnerability to cannabis exposure.<sup>7</sup> For example, pubertal rats treated with a cannabinoid agonist showed persistent deficits on object recognition tasks, whereas adult rats did not.<sup>8,9</sup> Accumulating evidence in humans parallels the animal findings.<sup>9</sup> For example, several studies have shown that earlier age at onset of cannabis use is associated with greater neuropsychological impairment,<sup>10,11</sup> and a 2012 population-representative longitudinal study<sup>12</sup> documented that adolescent-onset (but not adult-onset) persistent cannabis users showed neuropsychological decline from ages 13 to 38 years.

Neuroimaging investigations of adolescent and adult cannabis users have yielded somewhat inconsistent findings. Recent reviews have demonstrated that there is fairly clear evidence of structural alterations in medial temporal (amygdala and hippocampus), frontal, and cerebellar regions associated with cannabis exposure.<sup>13,14</sup> However, another recent study<sup>15</sup> that carefully matched participants on alcohol intake reported no evidence of morphological brain alteration among adolescent or adult cannabis abusers, suggesting the possibility that comorbid alcohol use could explain some of the morphological alterations observed in prior research. There is also some evidence that cannabis users have impaired neural connectivity. For example, a study<sup>16</sup> of adults with long histories of heavy cannabis use showed evidence of decreased connectivity in the right fimbria of the hippocampus (fornix) and the splenium of the corpus callosum and the commissural fibers. Finally, functional magnetic resonance imaging investigations have suggested that cannabis users show altered neural activity both in the resting state and during cognitive testing.<sup>14</sup> For example, male adolescent cannabis

## Does MJ affect:

- Neuro-cognition?
- Motivation?
- Psychosis?

# WHAT ABOUT PSYCHOTIC SYMPTOMS AND SCHIZOPHRENIA?

| Table                    | Summary of key studies linking cannabis and psychosis  |   |
|--------------------------|--|---|
| Study                    | Design   | Results   |
| Andréasson <sup>12</sup> | 15-year follow-up study of more than 45,000 Swedish conscripts   | Cannabis use by age 18 led to a 6-fold increase in the risk of schizophrenia later in life  |
| Arseneault <sup>13</sup> | Prospective longitudinal study of adolescent cannabis use and psychosis in Dunedin, New Zealand  | Those with early-onset cannabis use experienced more psychotic symptoms than controls   |
| Caspi <sup>14</sup>      | Secondary analysis of the influence of the <i>COMT</i> gene Val158Met variant on the development of psychosis among cannabis users in Dunedin, New Zealand | The presence of the Val allele led to an increased risk of psychosis in adulthood when coupled with a history of adolescent cannabis use        |
| Fergusson <sup>15</sup>  | 21-year longitudinal study of the link between cannabis and psychosis in a birth cohort in Christchurch, New Zealand                                       | Rates of psychotic symptoms were 3.7 and 2.3 times higher in cannabis-dependent individuals when measured at ages 18 and 21, respectively       |
| Henquet <sup>16</sup>    | Prospective cohort study of psychotic symptoms as a function of cannabis use and baseline psychosis predisposition   | Cannabis use at baseline increased the risk of psychosis (adjusted OR, 1.7); predisposition to psychosis significantly increased this effect    |
| Tien <sup>18</sup>       | Multisite US epidemiological study of the relationship between self-reported psychotic experiences and cannabis use  | Any cannabis use was associated with a 30% increased risk of psychotic experiences, while daily use was associated with a 2.4-fold greater risk |
| van Os <sup>19</sup>     | 3-year population-based prospective study of the effects of baseline cannabis use on the development of psychosis in the Netherlands                       | Baseline cannabis use was associated with the presence of psychotic symptoms (adjusted OR, 2.8)   |

*COMT*, catechol-O-methyltransferase; OR, odds ratio.

intoxication

## Cannabis Effects on Driving Skills

Rebecca L. Hartman<sup>1,2</sup> and Marilyn A. Huestis<sup>1\*</sup>

**BACKGROUND:** Cannabis is the most prevalent illicit drug identified in impaired drivers. The effects of cannabis continue to be debated, making proscription difficult. Historically, delays in detection, evaluating the inactive  $\Delta^9$ -tetrahydrocannabinol (THC) metabolite 11-nor-9- $\alpha$ -carboxy-THF-A, and polydrug use have complicated evaluations of driver impairment after

ingestion. Cannabis is associated with substantial driving impairment, particularly in occasional smokers. Future cannabis-and-driving research should emphasize challenging tasks, such as divided attention, and include occasional and chronic daily cannabis smokers.

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Risk of motor vehicle accident increase about 2x after smoking MJ. Critical tracking tasks, reaction times. Divided-attention tasks, lane-position variability all show MJ-induced impairments. Dose dependent. Even among more tolerant regular users, impairments persist.

view and evaluate the current literature on driving, highlighting the epidemiologic and experimental data. Epidemiologic data suggest a risk of involvement in a motor vehicle accident increases approximately 2-fold after smoking. The adjusted risk of driver culpability increases substantially, particularly with increasing THC concentrations. Studies that have used a biological matrix have not shown an association between cannabis and crash risk. Experiments show that drivers attempt to compensate for impairment slowly after smoking cannabis, but performance decreases with increasing task complexity. Driving increases lane weaving and impairment. Critical-tracking tests, reaction-time tasks, and lane-position variability show cannabis-induced impairment. Dose-dependent impairment in frequent smokers, compared to occasional smokers, shows impairment. Combining cannabis with alcohol enhances impairment, especially lane weaving.

**SUMMARY:** Differences in study designs frequently account for inconsistencies in results between studies. Participant-selection bias and confounding factors attenuate ostensible cannabis effects, but the association with MVA often retains significance. Evidence suggests recent smoking and/or blood THC concentrations 2–5

Nearly two thirds of US trauma center admissions are due to motor vehicle accidents (MVAs),<sup>3</sup> with almost 60% of such patients testing positive for drugs or alcohol (1). In 2010, 11.4% of Americans 12 years or older drove under the influence of alcohol, and 10.6 million drove under the influence of illicit drugs (2). Despite real or perceived impairment, individuals report a willingness to drive if there is a good reason (3, 4) or if they believe they are tolerant (5). Alcohol and cannabis are the drugs most frequently detected (6).

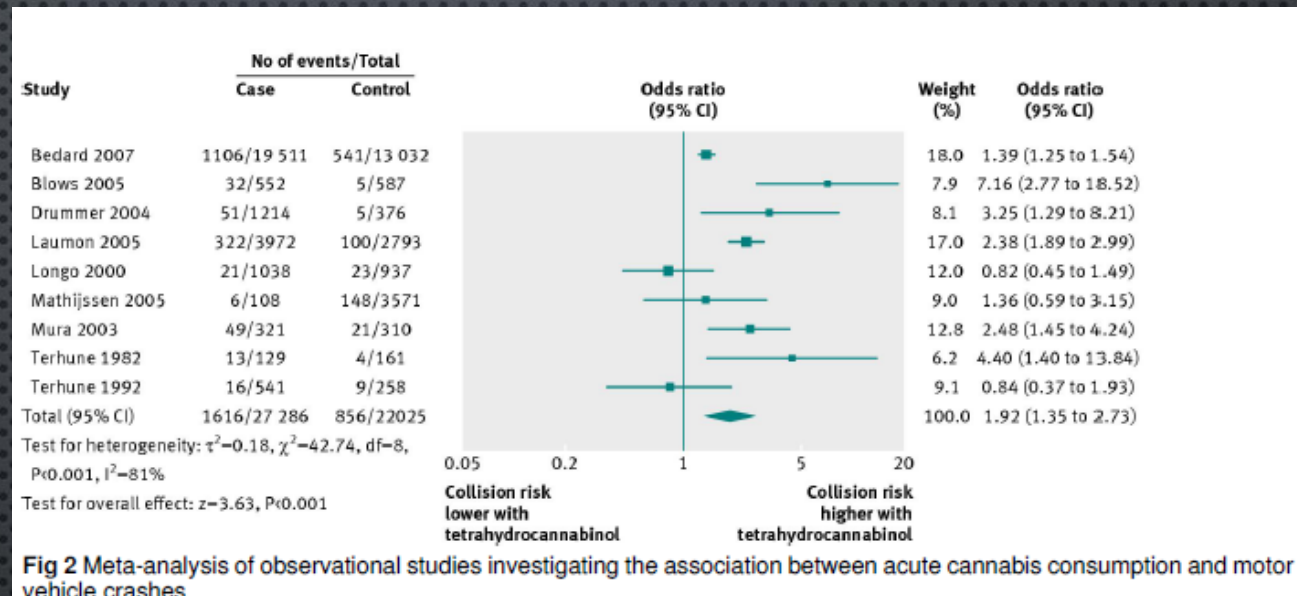
Cannabis is the most widely consumed illicit substance worldwide (2). In 2009, 125–203 million individuals 15–64 years of age ingested cannabis in the previous year (7). In the US in 2010, 6.9% of individuals  $\geq 12$  years old had smoked cannabis in the previous month (2). The 2007 National Roadside Survey reported cannabis as the most common illicit drug quantified in drivers' blood or oral fluid (OF), with 8.6% of nighttime drivers testing positive for  $\Delta^9$ -tetrahydrocannabinol (THC) (6, 8). Thus, driving under the influence of cannabis (DUIC) is a growing public health concern.

The acute psychological effects of cannabinoids include euphoria, dysphoria, sedation, and altered perception (9). The intensity of euphoria/dysphoria varies with dose, administration route, and vehicle; expectations of effects; and the cannabis smoker's environment and personality. Cannabis is associated with subjective physical discomfort and effort, as well as with lethargy (10). Acute cannabis intoxication produces dose-related impairment in cognitive and psychomotor functioning, and it can produce risk-taking behavior that can impair driving skills (11, 12). Dose refers to

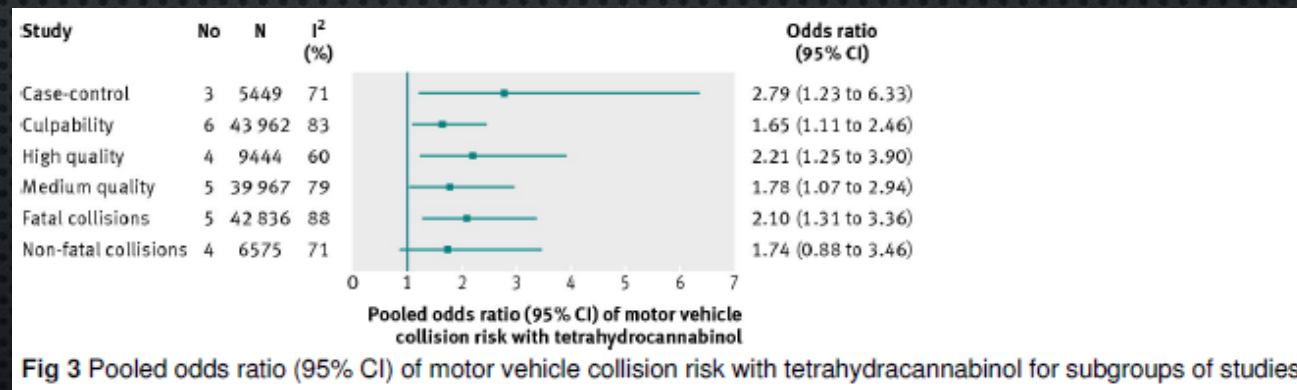
<sup>1</sup>Chemistry and Drug Metabolism, Intramural Research Program, National Institute on Drug Abuse, Bethesda, MD

# PUBLIC HEALTH RISKS OF MARIJUANA

## MOTOR VEHICLE COLLISION RISK OVER ALL STUDIES



## MOTOR VEHICLE COLLISION RISK BY TYPE OF STUDY



Asbridge, M., Hayden, J. A., & Cartwright, J. L. (2012). Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ: British Medical Journal*, 344.

## RESEARCH ARTICLE

# Correlates of Marijuana Drugged Driving and Openness to Driving While High: Evidence from Colorado and Washington

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## Results

Prevalence of past-year driving while under the influence of marijuana was 43.6% among

**Method:** Online survey of of past month MJ users in WA and CO states (N=865)

**Results:** Prevalence of past-yr driving under influence of MJ was 44%  
Prevalence of driving within 1 hour of using MJ 5+ times in past month = 24%

69% lower odds of driving if perceived risky  
37% lower odds of driving if had knowledge of MJ DUI laws

# Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado\*

Stacy Salomonsen-Sautel<sup>1</sup>, Sung-Joon Min<sup>1</sup>, Joseph T. Sakai<sup>1</sup>, Christian Thurstone<sup>1,2</sup>, and Christian Hopfer<sup>1</sup>

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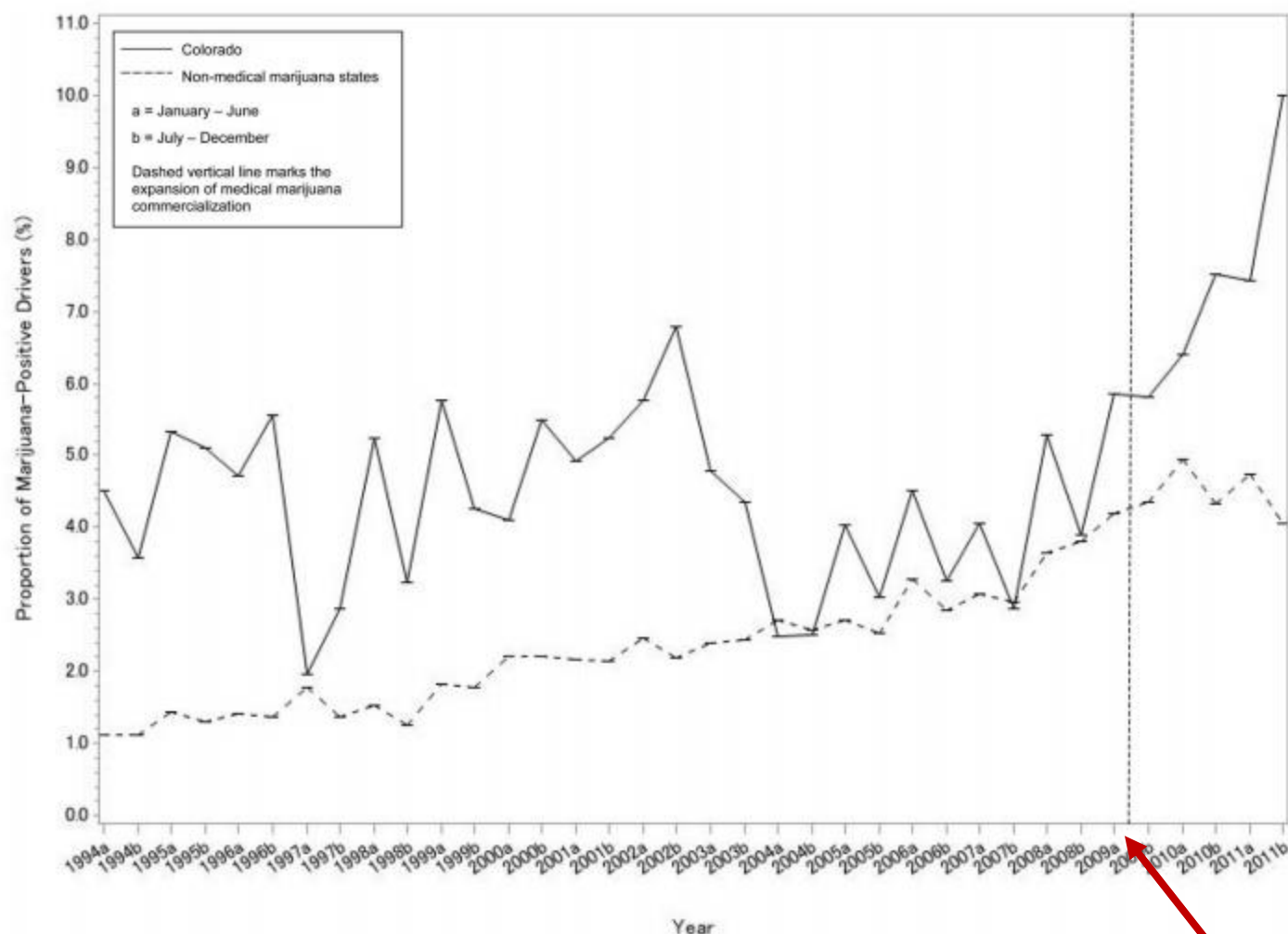
<sup>2</sup>Denver Health and Hospital Authority, Denver, CO, 80204

## Abstract

**Background**—Legal medical marijuana has been commercially available on a widespread basis in Colorado since mid-2009; however, there is a dearth of information about the impact of marijuana commercialization on impaired driving. This study examined if the proportions of drivers in a fatal motor vehicle crash who were marijuana-positive and alcohol-impaired, respectively, have changed in Colorado before and after mid-2009 and then compared changes in Colorado with 34 non-medical marijuana states (NMMS).

**Methods**—Thirty-six 6-month intervals (1994–2011) from the Fatality Analysis Reporting System were used to examine temporal changes in the proportions of drivers in a fatal motor vehicle crash who were alcohol-impaired ( $\geq 0.08$  g/dl) and marijuana-positive, respectively. The pre-commercial marijuana time period in Colorado was defined as 1994–June 2009 while July 2009–2011 represented the post-commercialization period.

**Results**—In Colorado, since mid-2009 when medical marijuana became commercially available and prevalent, the trend became positive in the proportion of drivers in a fatal motor vehicle crash who were marijuana-positive (change in trend, 2.16 (0.45),  $p < 0.0001$ ); in contrast, no significant changes were seen in NMMS. For both Colorado and NMMS, no significant changes were seen in the proportion of drivers in a fatal motor vehicle crash who were alcohol-impaired.



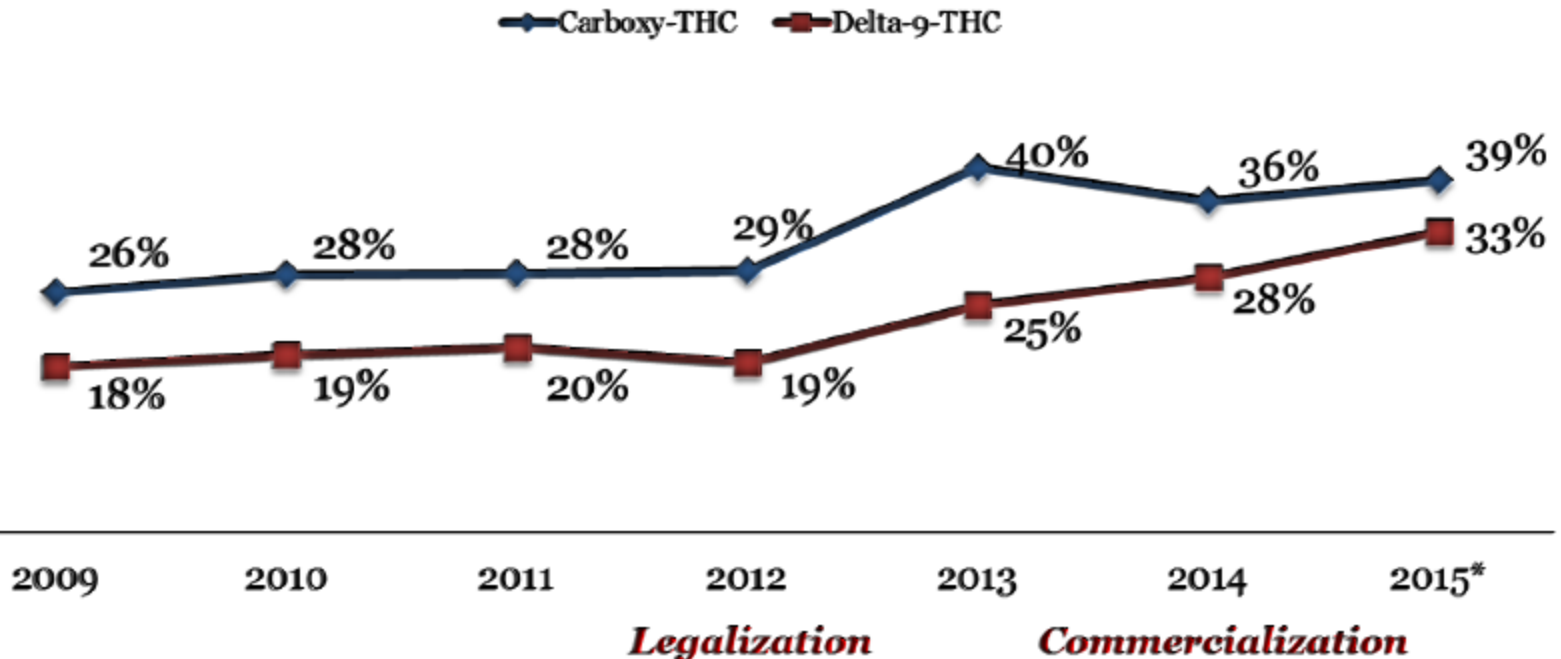
**Figure 2.**

Proportion of drivers in a fatal motor vehicle crash who were marijuana positive in Colorado and 34 states without medical marijuana laws from 1994–2011

Commercialization of medical MJ in CO

# WASHINGTON STATE REPORT

## Percentage of Total Driving Cases Positive for Carboxy-THC and Delta-9-THC 2009-2015\*

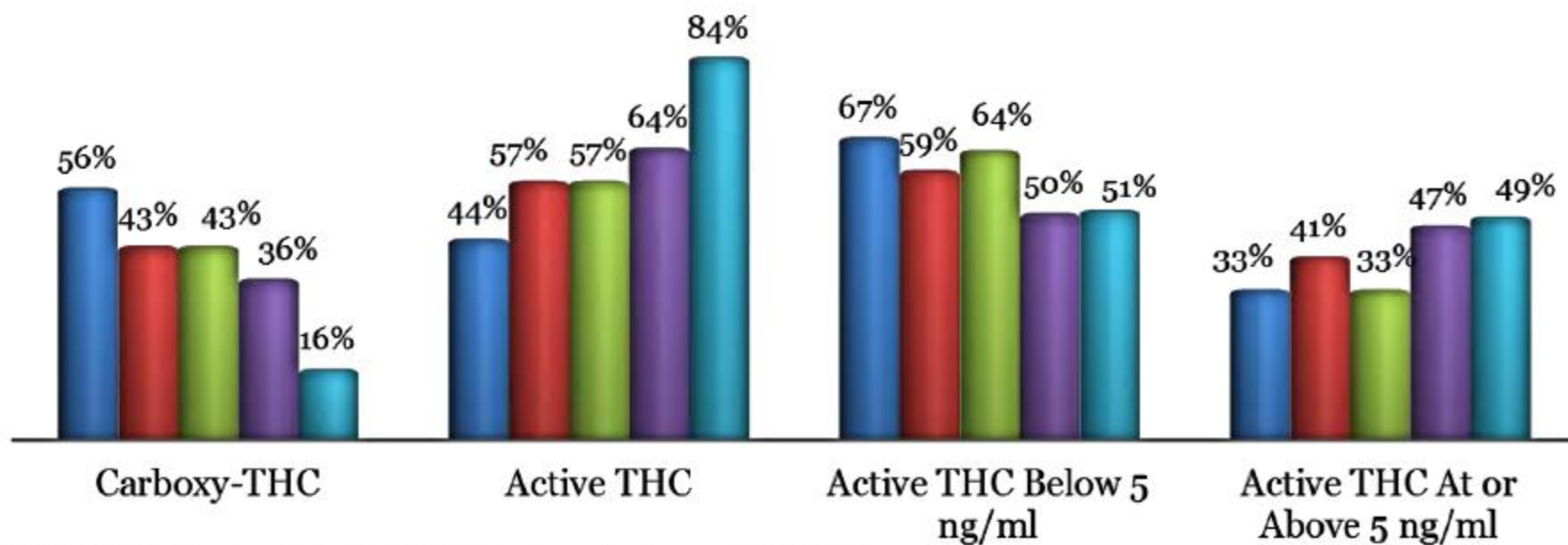


SOURCE: Washington State Patrol Toxicology Laboratory and NWHIDTA

2015\*: January through April 2015

## Drivers Positive for Any Cannabinoid

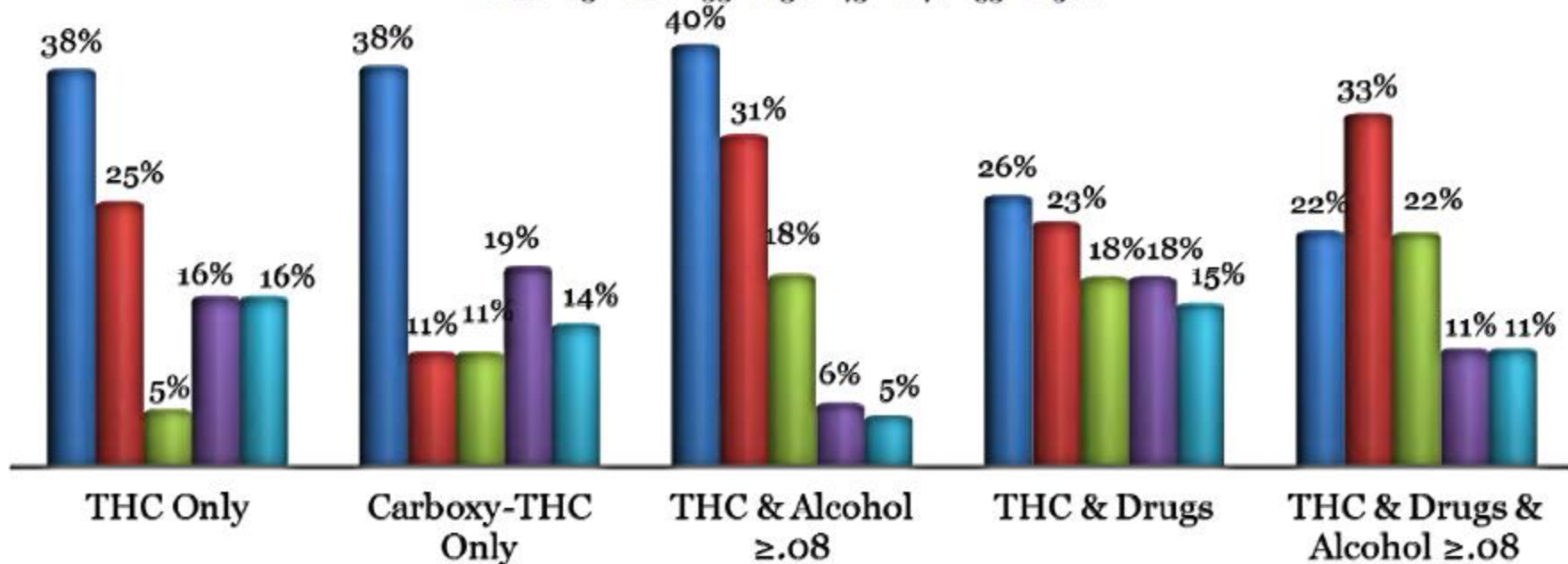
■ 2010 ■ 2011 ■ 2012 ■ 2013 ■ 2014



SOURCE: Washington State Traffic Safety Commission and NWHIDTA

## Drivers by Age

■ 16 - 25 ■ 26 - 35 ■ 36 - 45 ■ 46 - 55 ■ 56+



SOURCE: Washington State Traffic Safety Commission and NWHIDTA

# SUMMARY

- POTENTIAL PROS

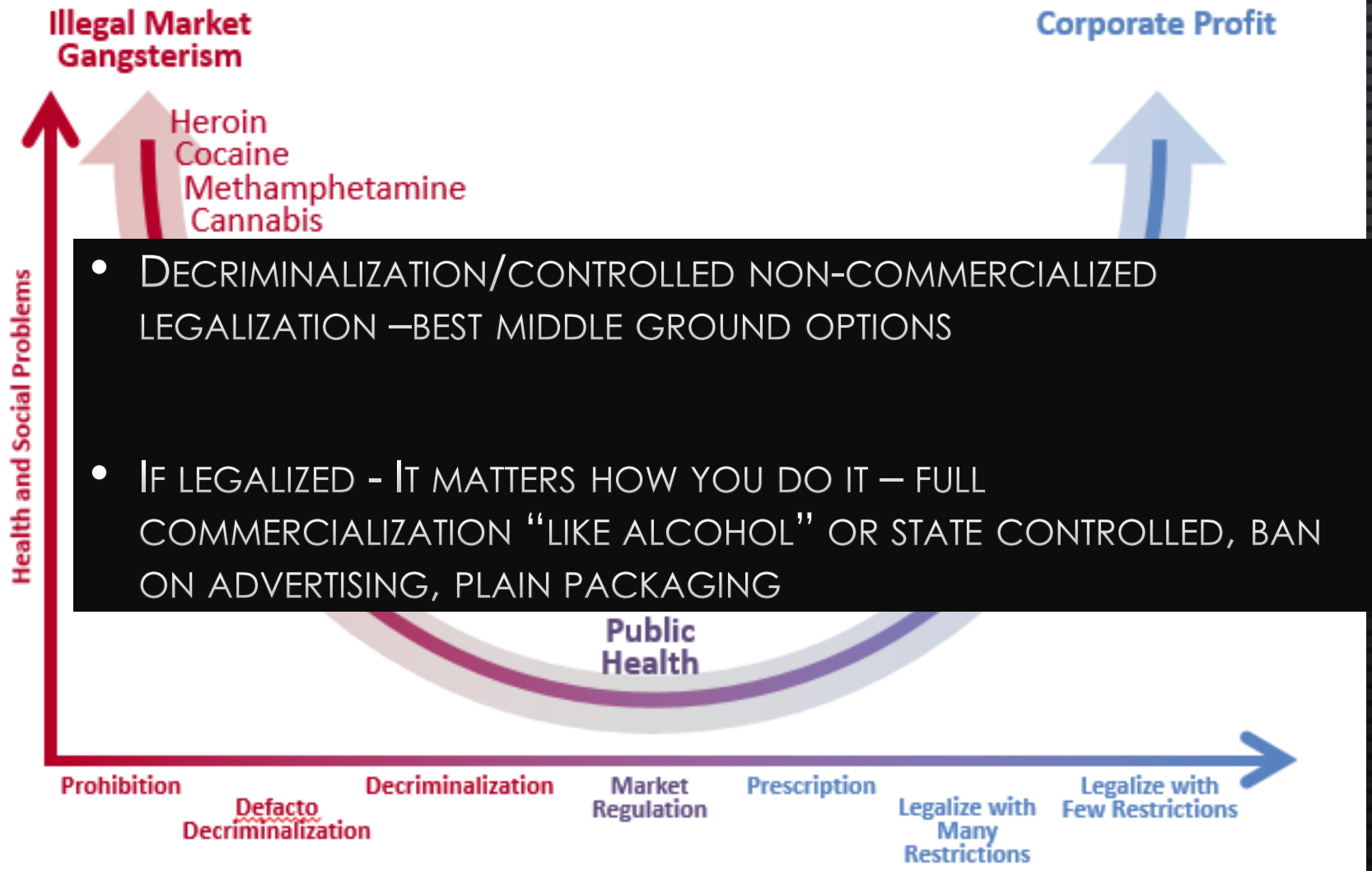
- LEGALIZATION MEANS IMPROVEMENTS IN PRODUCT QUALITY CONTROL
- ERADICATION OF ARRESTS TO DOE TO POSSESSION (IF 21 YRS +)
- MINIMIZATION/ERADICATION OF BLACK MARKET
- TAX REVENUE

- POTENTIAL CONS

- PUBLIC HEALTH AND SAFETY HARMS
- CONSUMPTION WILL INCREASE
- ADDICTION RATES WILL INCREASE AND HARMS RELATED TO ACUTE INTOXICATION (E.G., DRIVING ACCIDENTS) WILL INCREASE
- TOXICITY-RELATED POISONING AND NEUROCOGNITIVE EFFECTS AMONG CHILDREN AND TEENAGERS ARE LIKELY TO INCREASE
- ENFORCEMENT OF LEGALIZATION REGULATIONS WILL BE NEEDED – ARRESTS FOR VIOLATIONS (AND RELATED COSTS) COULD BE HIGH EVEN IF SUBSTANTIALLY LESS THAN ALCOHOL
- PRODUCTIVITY COULD GO DOWN IN THE POPULATION AS MORE PEOPLE COULD MISS WORK DAYS/UNDERPERFORM AT WORK CONTRIBUTING TO ECONOMIC INCREASED BURDEN

# SUMMARY

## Degree of Problems Associated with Various Policy Approaches to Addressing the Drug Problem



# ARGUMENTS FOR CANNABIS LEGALIZATION

- “WAR ON DRUGS” HAS FAILED
- 5% OF WORLD’S POPULATION -25% OF WORLD’S PRISONERS
- 2.5 MILLION LOCKED UP; ABOUT 500,000 OF WHOM ARE THERE FOR DRUGS
- RACIAL DISPARITIES IN INCARCERATION RATES AT SAME PREVALENCE OF USE
- LEGALIZATION WOULD REDUCE ARRESTS/CRIMINAL JUSTICE COSTS (2013- 41% OF ALL ILLICIT DRUG-RELATED VIOLATIONS WERE MJ POSSESSION; 6% FOR MJ SALE/MANUFACTURING)
- DEMAND IS HIGH- “GONNA DO IT ANYWAY” SO WHY NOT REGULATE IT AND MAKE IT SAFE?
- IT’S NOT BAD/AS BAD AS ALCOHOL/TOBACCO -EVEN GOOD FOR YOU (MEDICINAL)
- TAX IT AND BRING IN REVENUE FOR STATES

# SO, LEGALIZE?

- OF THE 2.5 MILLION PRISONERS IN US ABOUT 500,000 ARE THERE DUE TO DRUG LAW VIOLATIONS, **BUT ONLY ABOUT 40,000 OF THESE ARE MJ**
- THIS WOULD BE JUSTIFICATION FOR DECRIMINALIZATION NOT LEGALIZATION BUT EVEN SO, TO “END THE WAR ON DRUGS” BY LEGALIZATION OF MJ WON’T DO IT
- WHAT WILL HAPPEN IS THE REDUCTION ON THE ARRESTS ANNUALLY (FOR POSSESSION) IN THE US – ABOUT 700,000 REDUCTION IN ARRESTS ANNUALLY
- HOW TO LEGALIZE? INDUSTRY – MAJORITY OF MARKET IS HEAVY USERS/ADDICTED– (80% OF VOLUME USED IS BY 20%)
- IF WE MAKE IT MORE AVAILABLE AND ACCESSIBLE, CHEAPER, REMOVE SOCIAL STIGMA AND LEGAL PENALTIES AND HAVE INDUSTRY AGGRESSIVELY ADVERTISING IT, USE WILL INCREASE
- BUT WILL INCREASE USE CAUSE ANY REAL HARM TO PUBLIC HEALTH? WORKFORCE PRODUCTIVITY? CRIME?

# WHAT HAPPENS AFTER 30 DAYS OF ABSTINENCE?

- PSYCHIATRIC
  - IMPROVEMENT IN MOOD
- COGNITION
  - ↑ ATTENTION
  - ↑ EXECUTIVE FUNCTIONS

